Temporal Dynamics of Emotion Regulation

A fMRI study of neural activity and functional connectivity

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Abstract

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Emotion regulation strategies are thought to have differential impact on emotional experience as a consequence of when and how they interact with the emotion-generative process. These differences are thought to be reflected in the dynamics of the neural systems underlying emotion generation and emotion regulation. However, few studies of neural activity have hitherto been undertaken directly contrasting different emotion regulations strategies, and none have investigated the temporal dynamics of connectivity in emotion regulation. Therefore, the current study investigated the temporal dynamics of neural activity and functional connectivity during performance of cognitive reappraisal and expressive suppression. These strategies are thought to differ in when in the emotion generative process they are active. These differences are hypothesized be reflected in different temporal signatures and neural substrates. To investigate this 39 subjects of both genders underwent fMRI scanning while regulating their emotional response to 15 second disgust-inducing film clips using these strategies. Contrary to earlier findings, the current study found suppression- and reappraisal-related activity in both Early (0-5) and Late (10-15) periods of the film. The results concur with previous studies in indicating that Reappraisal is subserved by two distinct top-down appraisal systems, that affect the both perceptual and affective bottom-up appraisal systems. Suppression in turn was indicated to be two distinct networks, one motor control network and one conflict monitoring network hypothesized to be involved in mediating the conflict between the inhibitory motor control and prepotent emotional response patterns. The temporal dynamics and connectivity patterns were interpreted as supportive of this hypothesis. Further evidence was found that both of these strategies are characterized by activity in a region of the brain implicated in emotion-related control in a wide variety of studies. This is interpreted as evidence for the existence of a core emotion regulation network centred on the Inferior Frontal Gyrus, that affords emotion-related regulation through the setting of reference states for other, task-specific, control networks.

Preface

The present study is a part of the project *"Establishing the Neural Architecture of Emotion Regulation in a Normal Population"*, undertaken by the author under the supervision of associate professor Tor Endestad. This study was made possibly by a student research grant to the author by the Norwegian Research council, from January to December 2009. The author conceived of the study, designed the experiment. Recruitment of participants and data collection was performed during the Spring of 2009. All analyses presented in this thesis were performed by the author.

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Tor Endestad for allowing me the opportunity to embark on a research career in cognitive neuroscience, backing in the implementation of the study, feedback and guidance in the writing process of the current thesis, and above all for allowing me the freedom and responsibility needed to develop the skills and understanding necessary to undertake this project in the first place.

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"*Control thy passions, lest they take vengeance on thee.*"- Epictetus

1: Introduction

The campaign to correct Descartes´ error of emotion/cognition dualism has been rather successful in modern psychology and cognitive neuroscience. Most every aspect of cognition has been shown to be somehow infused with, modulated by or enhanced through emotional influence (Pessoa, 2008). Research has shown that human function in a range of disparate areas, from decision making (Bechara, H. Damasio, & A. Damasio, 2000, 2003) and moral judgments (Prinz, 2007) to primary visual perception (Phelps, Ling, & Carrasco, 2006) have emotional tributaries essential for adaptive function. In accordance with this, the long standing view of emotion as an impulsive, short sighted and fundamentally primitive influence has also begun to be corrected. Modern accounts of emotion instead emphasize emotions´ ability to focus our attention and prepare us for action in an efficient and adaptive manner (Barrett, Mesquita, Ochsner, & Gross, 2007; A. Damasio, 1994). There is therefore little doubt that emotions have a series of salutatory adaptive functions in our lives by guiding our behaviour and cognitive capacities towards pertinent goals.

However, there is also something to be said for the recommendation of the Stoic philosopher Epictetus. The ability to flexibly regulate and express ones emotional reactions are in many cultures thought of as a hallmark of maturity, and one of the primary demands placed on someone aspiring to the status of a responsible individual (Eisenberg, 2000). According to many of our shared myths, humanity has struggled with emotions and their regulation since time immemorial. Stories spanning from the sacking of Troy caused by the hubris of pride, to the fall from grace caused by the lust of Adam and Eve, and the original fratricide of Abel by Cain due to jealousy, all hint at the potentially calamitous influence emotions can have on our lives. The wisdom of these culturally transmitted warnings is evidenced by the fact that the dominance of unregulated emotion is characteristic of a wide range of psychopathological syndromes (Werner & Gross, 2010), and that disturbed emotion regulation is arguably a mediator of a range of social problems spanning from road rage (Denson, Pedersen, Ronquillo, & Nandy, 2009) to substance abuse (Cooper, Frone, M. Russell, & Mudar, 1995). Thus, it is evident that the same qualities that enable emotional reactions to adaptively shape our behaviour also allow them to wreak havoc on our lives if they are uncoupled from the individual's goals and allowed free reign.

1.1: Emotion regulation as a subject in psychology

In spite of emotion regulation having been a subject of legend, literature, and philosophy for

millennia, it is only relatively recently that significant strides have been made towards the development of empirically based models of this ability. In psychology, research on emotion regulation (ER) started in the clinical literature with descriptive studies of psychodynamic defence mechanisms. In the 1960´s this line of research inspired the empirical study of the factors that influence an individual´s ability to cope with stressful situations (e.g Lazarus, 1966). The generalization of the coping literature into the realm of general emotion functioning, has led to the study of ER being a major subject of psychology (Koole, 2009) and cognitive and affective neuroscience (Gross & Thompson, 2007). Despite there being an immense interest in the subject, there has yet to emerge a unifying theory of ER that guides the research being performed. This is evidenced by the variety of meanings the term *emotion regulation* might assume when looking within some fields (e.g. developmental psychology; compare (Cole, Martin, & Dennis, 2004) and (Eisenberg & Spinrad, 2004)) and between other fields (e.g. between adult and developmental psychology; Gross & Thompson, 2007).

While initially disheartening, this proliferation of definitions can be explained by the observation that the concept of emotion regulation encompasses a vast range of purposeful behaviour. For instance, while the term *regulation* might invoke the concept of an intra-individual, effortful and conscious process, this not necessarily an exhaustive definition of the subject. There is large body of literature indicating that emotion regulation occurs at both automatic and conscious levels of processing (cf. Mauss, Bunge, & Gross, 2007; Phillips, Ladouceur, & Drevets, 2008). In addition an equally large body of literature indicates that much, if not most, emotion regulation occurs in an inter-individual context, where individuals attempt to attune their emotional responses to societal norms or the emotional states of others (cf. Rimè, 2007). There is also evidence that the majority of ER strategies employed by children are qualitatively different from those employed by adults, and that much ER behaviour in childhood is in fact co-regulation of emotion by caregiver and child (e.g. Cole et al., 2004). Hence, it is not surprising that researchers focusing on specific aspects of emotion regulation tend to adapt their definitions to the subject of enquiry. Therefore, there is significant difficulty in establishing an all-encompassing definition of emotion regulation, based on what regulation means and how this regulation is manifested. As we will see in the next section, this difficulty is compounded by the fact that there is no clear consensus on what the object of regulation, namely emotions, actually are.

1.2: Emotion regulation and emotion theory

There is a long standing debate in the field of emotion theory between basic emotion

theorists (e.g. Ekman, 1992; Izard, 1992; Zajonc, 1984) and appraisal theorists (e.g. Lazarus, 1982; J. A. Russell, 1980; Scherer, 2001). The former conceive of emotions as evolutionarily selected reflexive reactions to emotionally significant stimuli. The latter in turn conceive of emotions as being the consequences of cognitive appraisals of the emotional significance of a stimulus as defined by the influence of active goals, prior experiences, and context on an individual.

In relation to emotion regulation, this debate is of great importance, since the model of emotion one endorses has an impact on what is entailed by saying that an emotion has been regulated. If, for instance, one accepts a basic emotion framework, this constrains the functioning of emotion regulation to a post-hoc process, occurring after the emotional response proper. This is because it is a theoretical axiom of basic emotion theory that emotions are modular, reflex- like and, once elicited, impossible to interrupt (Matsumoto & Ekman, 2009). Hence this theoretical view prescribes that emotion regulation must be the regulation of the consequences of emotion rather than a regulation of the emotional response itself. So, the basic emotion inspired researcher might find it difficult to conceptualize ER as anything except the avoidance of emotion eliciting stimuli, or the control of emotion-related behaviour. If, however, one accepts an appraisal theory of emotions, one is left with the difficulty of differentiating the initial bottom-up emotional appraisal from the regulatory top-down influence exerted by the individual. Based on this it has been proposed by one influential appraisal theorist that all emotions are, in fact, regulated (Frijda, 1986). This is because, in appraisal theory, every emotional appraisal is thought to regulated and co-determined by active goals and past experience. So, the appraisal theory inspired ER- researcher, might find it difficult to find an emotional reaction that is complex enough to be open for regulation, while at the same time being "basic" enough to be relatively unregulated.

Summarizing, the traditional theories of emotion are both ill suited to address the phenomenon of emotion regulation. This, in part, is a consequence of basic emotion theory focusing on identifying the components of discrete pure emotional reactions that by definition are unregulated. On their part, the appraisal theory is focused explicitly on the contextual and contingent aspects of emotion, that by definition are regulated. Thus neither afford a theoretical framework particularly conducive for research in emotion regulation.

1.3: A working framework: Neurologizing emotion and emotion regulation

While the field of emotion theory is far from reaching a consensus on the exact nature of emotions, one promising avenue of approach for ameliorating the differences between these

diametrically opposed theoretical positions in actual emotion research is what has been called "neurologizing the psychology of affects" (Panksepp, 2007). This research strategy entails accepting both theories, *prima facie*, as complementary, and deciding which of the theoretical positions best explains a specific subject of emotion research by referring to the available data on the physiological processes and neural networks involved. A similar approach, named Social Cognitive and Affective Neuroscience (SCAN; Lieberman, 2006) has been extensively employed in the study of emotion regulation. This line of research has focused on synthesising and testing work on emotion regulation from different fields of psychology (such as social, developmental and personality psychology), and constraining models and hypotheses garnered from these fields by reference to physiological measures (such as skin conductance response (SCR)), neuropsychology (e.g. lesion studies) and neuroimaging methods (such as functional magnetic resonance imaging (fMRI) and event- related potentials (ERP)).

The results presented in this thesis is the first instalment of a larger study, the goal of which is to establish a unified causal model of the neural network underlying emotion regulation in a normal population using the methodological framework of SCAN. Before presenting the study and results proper, its theoretical and empirical foundations will be presented in concert with the guiding hypotheses for the study.

2: Theoretical and empirical foundations

2.1: The modal model of emotions: An integrative framework for emotion research

As the current study is primarily focused on emotion regulation, rather than emotions in and of themselves, it is advisable to adopt a model of emotion that is inclusive of both the earlier mentioned positions, while not giving precedence to either. One model that has been proposed to strike such a balance is the *modal model of emotion* (Figure 1), which is an integrative account of emotional processes that attempts to account for most of the lay intuitions underlying our understanding of emotion, as well as the strengths of both traditional accounts of emotion (Barrett, Ochsner, & Gross, 2007). This model proposes that an emotional episode begins with a psychologically relevant stimulus or situation (external happening or internal thought) that is attended to in various ways. This gives rise to appraisals, which involve judgements of the situation's familiarity, valence (good/bad), and goal relevance, among other things (see Ellsworth & Scherer, 2003 for a comprehensive account). These appraisals, in turn, give rise to emotion response tendencies, ranging from slight anxious uneasiness to full-scale outbursts of emotion (such as

anger) with 1) vivid emotion experience, 2) behavioral responses (e.g. flared nostrils, furrowed eyebrows), and 3) a host of powerful physiological changes (e.g., red face, increased heart rate). These three points; together constituting a coordinated change in *experience*, *behavioural response* and *physiological activation*, are the central components defining an emotional reaction in this model. Because emotional reactions often change the situation that gave rise to these responses in the first place, the model incorporates a feedback loop in which the emotional response modifies the stimulus (i.e. situation). This recursive aspect captures the ability of emotions to bring about their own up- or down-regulation through changing the environment, which again alters the emotional significance of the situation/stimulus. An example of this can be when someone becomes angry after an innocuous incident and others see this anger, it may arouse fear and make them more likely to avoid further interaction, thus changing the situation in a manner that alters its emotional content.

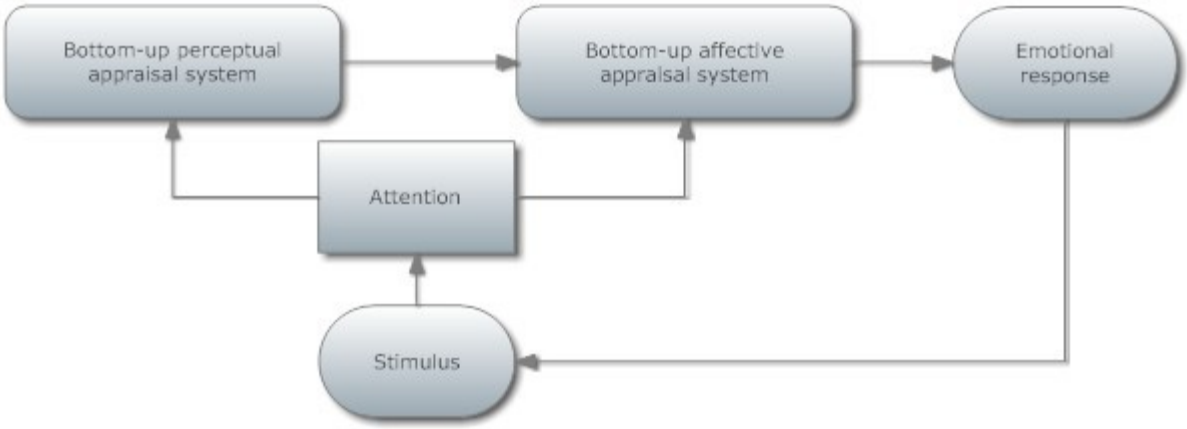


Figure 1. The modal model of emotion

Of special importance for the current study is that this model is silent on the finer points of basic emotion theories and appraisal theories. Rather it is based on only two core assumptions 1) that there is a small and discrete set of emotions or emotional dimensions that emotional reactions map onto and 2) that emotion generation is automatic. Both of these assumptions are common to either of the traditional theoretical frameworks (Barrett et al., 2007). Another point is that it does not address the relationship between emotion and cognition, and therefore does not separate emotional processes from cognitive processes on *a priori* grounds. Rather, it treats emotion and cognition as processes that compete for the same resources (e.g. attention or executive resources), and therefore conceptualize emotions (but not emotional reactions) as potentially malleable and adaptable to the individual's ongoing goal achievement. Emotional processes are, however, privileged, in that they possess what has been called “control precedence” (Frijda, 1988). In the model this aspect is captured by the direct flow of information from an attended stimulus directly to

the bottom-up appraisal system (BAAS), allowing an emotional reaction to be elicited without the involvement of the bottom-up perceptual appraisal system (BPAS).

This distinction between the BPAS and BAAS, and the contention that it is possible to engage the BAAS without the BPAS, is based on work showing that there are two different and distinct networks for processing of emotions (LeDoux, 2000). One network, known as the "low-road", supports rapid, but coarse, processing of emotional information. The other is known as the "high-road" and employs common perceptual processing areas. This network supports the fine grained processing of details and categorization of stimuli. In contrast to the rapid "low-road", the "high-road" consist of a series of processing stages with each stage adding increasingly more complex analysis of incoming information, ultimately resulting in a conscious perception, and consequently adding processing time. The existence of these parallel processing routes allow emotional processes to interrupt ongoing goal pursuits and supplant these with goals relevant to the emotion inducing stimulus. This happens without conscious awareness prior to the emotional response. Examples of such interruptions are the startle and fight- or- flight behavioural response patterns seen when exposing an individual to stimuli associated with potential threat. These responses interrupt behaviour and imposes a readiness to respond to the emotion eliciting stimulus. Thus, by way of the swiftness of the "low road" of processing, emotional reactions have precedence in deciding the behaviour of the individual. These reactions can in turn serve as co-determinants of a new emotion generation cycle, as described above. This highlights another important aspect of this model, namely its compatibility with a notion of emotions as dynamic processes that evolves over time, rather than simple reflexes. This allows the model to account for emotional events better than the traditional accounts, since these tend to (pace Matsumoto & Ekman, 2009) provide accounts of emotions as temporally circumscribed entities that are evoked by equally circumscribed events.

In summary, based on this model it is possible to propose a sequence of processes within an emotion generation cycle that 1) rapidly evaluate the potential of a stimulus to be emotionally significant, 2) encode sequences of behaviour and events that predict the occurrence of reinforcing stimuli, and 3) provide contextually informed elaborations of these evaluations that inform decision-making and the subjective experience of the emotional significance of a stimulus (Grandjean & Scherer, 2008). The first two of these points are performed by the BAAS, while the latter is performed by the BAAS and the BPAS in tandem. In addition, the model predicts that the dynamics of the emotion system will be affected by the previous states it was in, such that

modulating an early emotion generation cycle in an extended emotional event will have long- term consequences for the activity of the system as a whole. Hence, an emotion regulation strategy aimed at altering emotional appraisals of an extended event will likely have to impart its effects relatively early to be effective in altering character of the emotional event. As we will see in the next section, this coincides with what is predicted by one popular theory of emotion regulation.

2.2: Theories and models of emotion regulation

2.2.1: The process model of emotion regulation

Emotion regulation is for present purposes defined as *a special form of self-regulation that involves the attempt to modulate an emotional process or subcomponents of the process in order to bring them in line with with a goal representation or reference state* (Gross, 1998a; Magen & Gross, 2010). Therefore, ER as conceptualized here involves 1) an emotional reaction, 2) the conscious and volitional setting of an emotional reference state different from that of the emotional reaction and 3) an implementation process modulating the emotional reaction to bring it in line with the reference state.

Much of the recent work on emotion regulation in cognitive psychology and cognitive neuroscience has followed the process framework proposed by James Gross (1998). In this seminal article Gross identified five central modes of emotion regulation strategies. These can, with respect to a given cycle of emotion generation, be termed either *response-focused* or *antecedent-focused*. In other words one can broadly separate strategies into those that focus on regulation of emotional responses and those that focus on the processing that precede and are formative in the elicitation of an emotion. Research following this framework has focused on two commonly employed (Gross, Richards, & John, 2006) strategies of conscious emotion regulation: the response-focused strategy of *suppression* (modulation of expression, i.e. regulating emotions by preventing their expression) and the antecedent-focused strategy of *reappraisal* (cognitively based change; i.e. regulating emotions by actively altering ones appraisals of the emotion provoking stimulus or situation). Figure 2 illustrates where in the emotion generation process each of the ER strategies investigated in this study are hypothesised to have their regulatory effects in relation to the modal model of emotion.

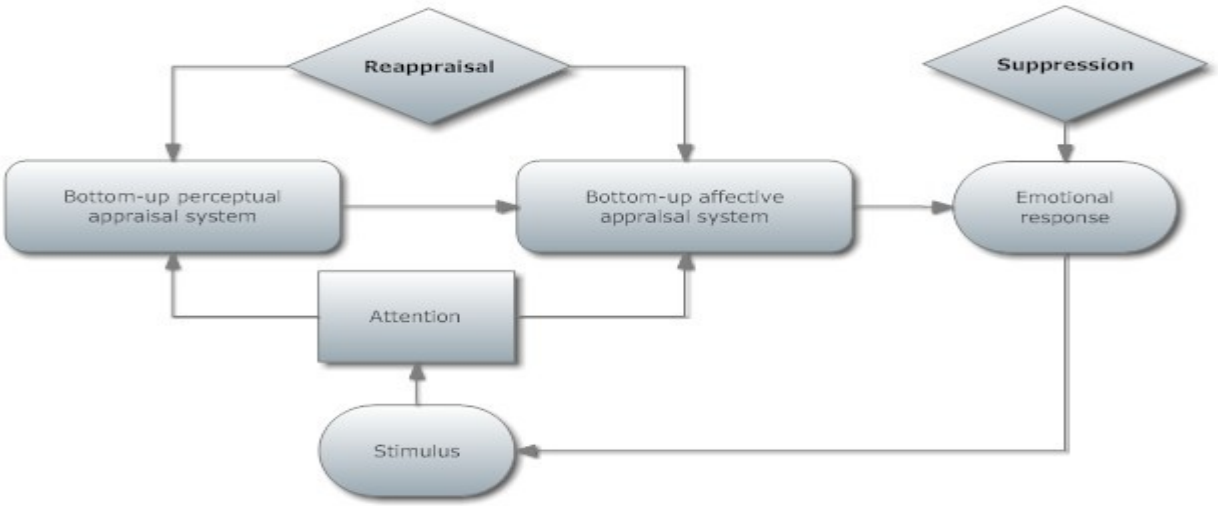


Figure 2. An adaptation of the process model of emotion regulation proposed by Gross (1998)

2.1.1.1: The temporal dynamics of reappraisal and suppression

The process model of emotion regulation predicts that antecedent-focused and response-focused strategies will impart their regulatory effects in different stages of the emotion generation process. Reappraisal, being an instance of the former, is predicted to have its effects early in the emotion generative process before the emotional response has been elicited. Suppression, being an instance of the former, will have its effects only after the emotional response has been elicited. A recent study (Goldin, Mcrae, Ramel, & Gross, 2008) interpreted this as giving rise to differential temporal dynamics for each of the strategies. On their view reappraisal involves early selection and implementation of a cognitive strategy that diminishes emotion without the need for sustained effort over time. Suppression, in contrast, involves increasing efforts as the emotional event unfolds to actively inhibit prepotent emotional behaviour as it arises in response to emotion-inducing stimuli. Given the differences of these two strategies with regards to their focus on different parts of the emotion process and their different temporal dynamics, it is to be expected that they have different consequences on the components of emotion mentioned above, i.e. experience, expression and physiology. As will be seen in the next section, this has been found to be the case.

2.1.1.2: The consequences of reappraisal and suppression

Reappraisal and suppression have been extensively studied since the formulation of the process model of ER, and they have been shown to have the predicted diverging effects. Reappraisal has been shown to effectively change emotional experience, with physiological stress-responses and emotional expression aligning to the subjective affective experience (Gross, 1998b). Suppression has been shown to effectively inhibit emotional expression, decrease positive affect

(Gross & Levenson, 1997), variably slightly decrease (Goldin et al., 2008) or have no effect on subjectively experienced negative affect (Gross, 1998b; Gross & Levenson, 1997), while increasing physiological stress-responses, and impairing cognitive capacities, such as memory (Richards & Gross, 2000). The tendency to preferentially use of these strategies have also been found to have differing consequences for the individual. Habitual use of reappraisal as an ER strategy is correlated with increased life satisfaction, reduced daily stress and better social functioning, while the opposite is true for the suppression strategy (John & Gross, 2004). The reason for this divergence of both short- and long-term effects can be gleaned from an examination of their functional components and architecture, i.e. what systems underlies each strategy, and how these systems interact during attempted regulation, which will be the subject of the following sections.

2.2.2: The functional components and architecture of cognitive reappraisal

Reappraisal is a complex ER strategy involving 1) the generation and maintenance of a strategy for the *cognitive reframing* of an emotional event, 2) *mediation of conflict* between the top-down interpretation of an emotional stimulus and the BAAS driven emotional impulse, and 3) the *reinterpretation of internal states* with respect to the stimulus that elicited it (Ochsner & Gross, 2004). It is therefore unlikely to be implemented by a single, unitary system. Rather, it has been proposed that emotion regulation through cognitive reappraisal of emotions (RE) is subserved by two distinct systems (see Figure 3): 1) the *Description Based Appraisal system (*DBAS), and 2) the *Outcome-based Appraisal System* (OBAS). The DBAS is involved in RE by i) consciously formulating, generating and implementing cognitive ER strategies based on the reinterpretation of the emotional significance of stimuli through the alteration of it´s description (i.e. changing ones appraisal of the stimuli) and ii) monitoring the efficacy of and mediating conflict between the regulatory intervention and emotional reactions. While the DBAS is thought of as the primary component of the reappraisal strategy, the regulatory effects of the DBAS are in the form of conscious reformulation of appraisals, and thus are relatively far removed from the automatic and relatively simple appraisals driving the bottom-up affective appraisal system (BAAS). Therefore the effects of the DBAS are posited to be mediated by 1: modulation of bottom- up perceptual appraisal systems (BPAS) and 2: direct communication with the OBAS.

The OBAS in turn is involved in reappraisal by changing the reinforcement contingencies of emotional stimuli and thus reinterpretation of the internal states associated with this stimulus. Relatively automatic modes of emotion regulation are thought to be primarily subserved by this

system, and it is therefore not a system specific to RE alone, but rather has been associated with a variety of emotion-related regulation tasks (Ochsner & Gross, 2007, 2004). One example of an emotion-related regulatory process that has been associated with the OBAS is extinction learning. Extinction learning is critically dependent on the learning of new associations for conditioned stimuli, which is to say that it depends on the altering of the reinforcement properties of a stimulus. Recent studies (Delgado, Gillis, & Phelps, 2008; Delgado, Nystrom, Fissell, Noll, & Fiez, 2000; Phelps, Delgado, Nearing, & LeDoux, 2004) support this contention, indicating that emotion regulation through RE relies on many of the same automatic mechanisms underlying associative extinction learning (Phelps, 2006).

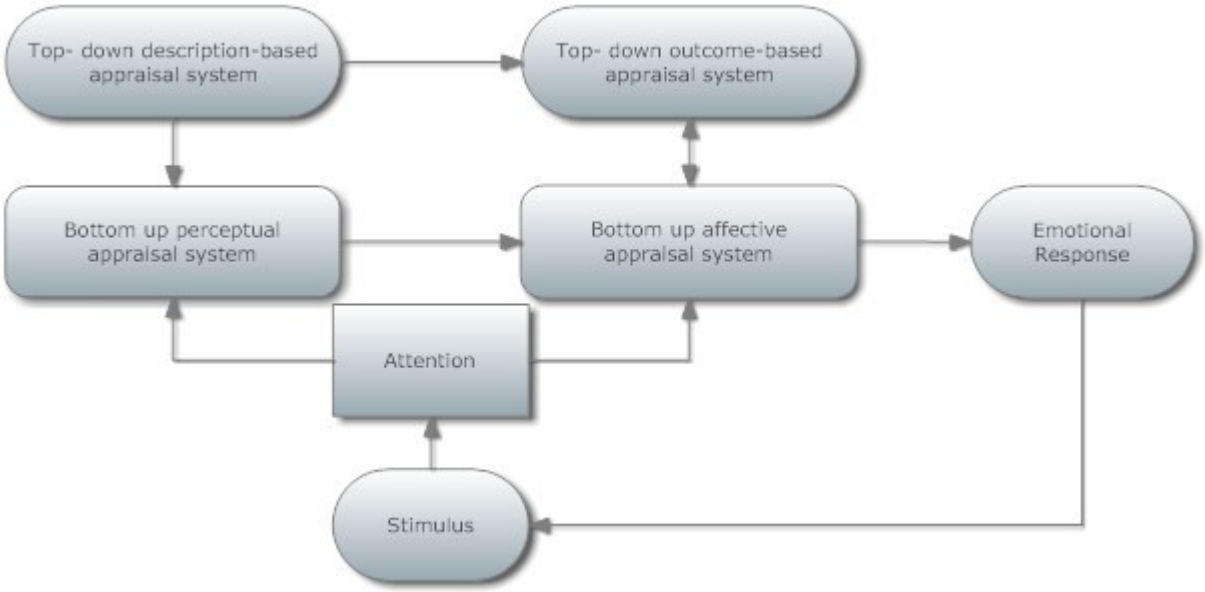


Figure 3. The functional architecture of cognitive reappraisal according to Ochsner & Gross (2007)

Thus, according to this model, it is possible regulate emotions through reappraisal in two ways: First, the DBAS acting alone can modulate emotional activity through the active reinterpretation of the emotionally significant perceptual aspects of the stimulus through influencing the bottom- up perceptual appraisal system (BPAS). This again might engage the bottom- up affective appraisal systems (BAAS), thus modulating these systems and thereby the emotion generative process. Second, when the DBAS and OBAS are working in concert, the DBAS can in addition to modulating the DBAS, engage the OBAS, thereby effecting change in the emotional meaning of a stimulus and providing an active override of the reinforcement properties of the stimulus.

Until now, we have focused on ER as a static phenomenon that is evoked to a single generated emotional "pulse". The modal model of emotion and the process model of emotion regulation both give predictions with regards to the temporal dimension of RE, however. Based on these models, previous work (Goldin et al., 2008) anticipated that RE would have its effects early in an emotional event, on account of it being an antecedent-focused ER strategy. This allows it to intervene early in the emotion-generative process, swiftly and efficently modulating emotional appraisals. Thus, as mentioned earlier, RE should result in diminished emotion without a need for sustained effort, on account of the stimulus being successfully reappraised and therefore no longer emotion-inducing. This interpretation is also in accord with what would be predicted from the dynamics of the modal model of emotion alone, as previously mentioned.

In summary, this model proposes that cognitive reappraisal implements direct modulation of primary affective appraisal systems through the active recruitment of both basic perceptual appraisal systems and context sensitive top- down emotional appraisal systems. It does this through the engagement of a specific conscious, description based appraisal system. This can modulate both perceptual appraisal systems and systems involved in the contextualization and automatic regulation of emotion. Thus ER by means of cognitive reappraisal, is an instance of 1) perceptual modification of the emotional stimuli and/or 2) volitional modulation of the reinforcement properties of affective stimuli that leads to changes in the properties of the emotional event, and therefore the emotional reaction. In addition, these regulatory effects are of such a nature as to allow a relatively early and permanent intervention without the need for prolonged activity over an extended emotional event.

2.2.3: The functional components and architecture of expressive suppression

In spite of the plethora of behavioural studies of suppression, there has yet to be proposed an explicit model of functional architecture underlying the strategy. It is, however, possible to draw upon the extensive literature on cybernetic process models for general self-regulation of behaviour to propose the necessary components of such regulation processes. ER through suppression can be thought of as a case of inhibitory behavioural regulation, based on an external goal state. Earlier work inspired by general systems theory (e.g. Carver & Scheier, 1998; Powers, 1974) has proposed that the essential components of a behavioural self-regulation network is 1) reference state that serves as a criterion for evaluating the success of the controlling influence, 2) a system that executes controlling influence on the behaviour producing systems, and 3) a comparator that checks for discrepancy between the goal state and the actual behaviour. Combining these components yields a regulatory network that maintains and corrects the implementation of the controlling influence on

the regulated system for as long as the reference state remains active. Figure 4 shows a self-regulation circuit coupled with the modal model of emotion generation, which serves as the working model of suppression for the current study.

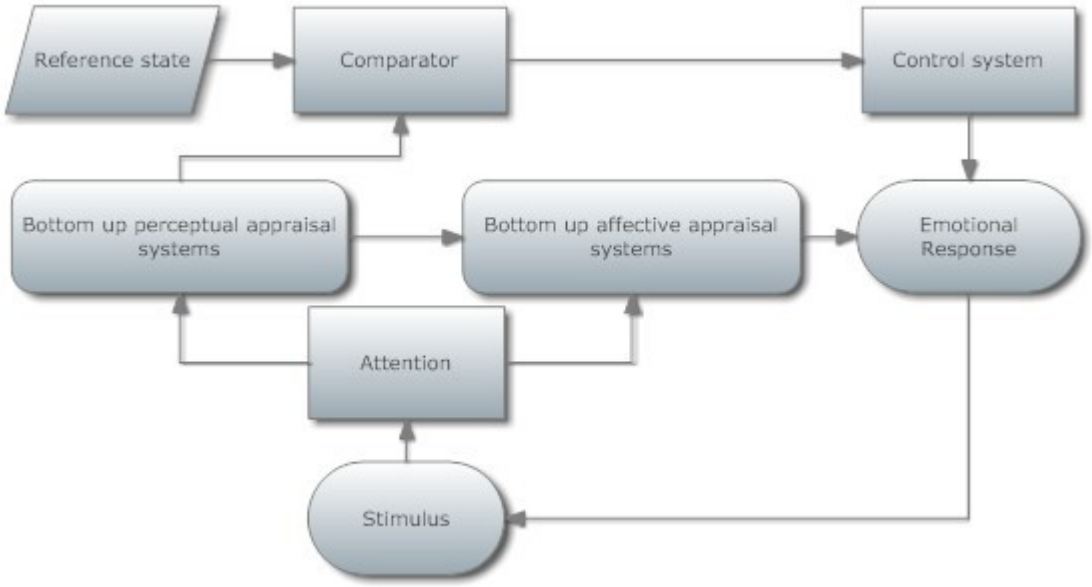


Figure 4. A working model of the functional architecture of ER through expressive suppression.

According to the process model of emotion regulation the suppression of emotional expression has its effects exclusively on the emotional response. Thus, the current model has no direct links between the control system and the BAAS, reflecting no direct modulation affective appraisal systems. This, however, does not preclude the possibility of suppression having an influence on emotion dynamics, since the expression of an emotion is an essential component of the emotion construct in the modal model of emotion. This is the case, as has been mentioned earlier, with SE being associated with changes in both emotional experience and emotion-related physiological responses. If the working model is correct it should be possible to explain these findings. This can be done by examining to the temporal dynamics of SE.

First, as has been mentioned, SE has been shown to reliably reduce positive affect (Gross & Levenson, 1997), and (less reliably) negative affect (Goldin et al, 2008). According to the facial-feedback hypothesis (e.g. Buck, 1980), skeletal muscle feedback from facial expressions plays a causal role in regulating emotional experience and behavior. Thus, by inhibiting the expression of emotion one influences the regulatory effects they afford. The exact nature and function of this regulatory influence is still a subject of debate, but well controlled studies (e.g. (Davis, Senghas, & Ochsner, 2009) indicate that facial expressions feed back into the emotion-generative process,

amplifying subjectively experienced affect. Accordingly, inhibiting facial expression removes this feedback loop, resulting in less experienced affect, explaining the reported reductions in experienced affect.

Second, SE has been shown to result in increases in physiological arousal measures, such as SCR and heart rate (Gross & Levenson, 1997). It is possible that this is a consequence of SE inducing a mismatch between the control precedence component of the emotional reaction, prescribing emotional behaviour, and the top-down control of expression. This can be thought of as an instance of a conflict between response tendencies requiring effortful executive control to resolve. This has been shown in earlier work to increase physiological activity in a manner reminiscent of that observed in the literature on suppression (compare e.g. Gross & Levenson, 1993; Kobayashi, Yoshino, Takahashi, & Nomura, 2007). This is also in accord with an earlier study of the temporal dynamics of SE (Goldin et al., 2008). The authors of this study predicted that SE should have effects only late in an extended emotional event, on account of it being a response-focused ER strategy, and found results that supported their hypothesis. Thus, increased physiological arousal might reflect conflict between the prepotent emotional response and the top-down regulatory influence, that is amplified over time by persistent activation of the BAAS by the emotional stimulus.

Thus ER by means of expressive suppression is possible to describe a process that consists of 1) an early interruption of the feedback- loop between emotional expression and emotion experience and 2) the possible induction of a conflict between response tendencies, requiring effortful executive control to resolve, with increasing conflict as the emotional event unfolds.

3: Neural foundations

Hitherto we have discussed emotion regulation with relation to theoretical models about how and when regulation will occur with respect to the modal model of emotion. Behavioural, psychophysiological and correlational studies all point in the direction that reappraisal and suppression have vastly different concomitants, indicative of them having different time-courses and different effects on emotional processes. A way of probing this issue further is with reference to the neural networks underlying the respective strategies and the dynamics of these networks during the implementation of ER. Before discussing the findings from research on these topics it is prudent to provide a introduction to the methods mainly applied in such research, and in the current study.

Much recent work on the neural foundations of emotion and emotion regulation has been performed using functional magnetic resonance imaging (fMRI). Briefly, fMRI measures neural activity indirectly, by way of the blood-oxygen-level-dependent (BOLD) signal. This signal is a consequence of increased blood-flow to areas of the brain where there is increased neural activity. (Logothetis & Wandell, 2004). fMRI can provide millimetric resolution spatial maps of BOLD signal changes in the brain with a temporal resolution on the scale of seconds.

There are multiple ways of using these images to infer task- related changes in brain activity. Commonly, fMRI experiments employ a subtractive logic, where two or more experimental conditions are contrasted against each other. This allows one to identify areas of the brain that were measured to have relatively more BOLD signal in one condition relative to another, and, by implication, that were relatively more active during that condition. These analyses afford themselves to investigating the *functional segregation* of the brain, i.e. what areas are involved in what tasks. Another line of analyses methods are geared towards investigating the *functional integration* of brain areas, i.e. how different specialized brain areas interact and influence one another during the performance of a task. Methods for examining functional integration can be separated into those that investigate *functional connectivity* and those that investigate *effective connectivity.* The former is defined as correlations in the timing of activity between spatially remote neurophysiological events, while the latter investigates the influence one neural system excerts on another (Friston, 1994). The main difference between these two forms of connectivity is that investigations of functional connectivity yield results that warrants one to make claims only about the covariance of activity between regions, while the latter explicitly models the causal influence a region has on another.

Investigations of functional segregation and integration play a complimentary role in the understanding of the neural bases of a psychological phenomenon. The former plays a crucial role in establishing what network of areas are involved in a task, while the latter gives important insight into the dynamics of this network. In the discussion of the neural bases of emotional processes and emotion regulation and for the remainder of the thesis, the term *activation* will be used to denote relative increases of BOLD-signal in a region, while the term *connectivity* will be used to denote changes in covariance of BOLD-signal between regions.

3.1:The neural bases and temporal dynamics of emotional generation

The modal model of emotion, reviewed above, posits that there should be systems involved

in 1) primary emotional appraisals and reactions, 2) perceptual emotional appraisals. These systems are proposed to be largely independent, and involve different sorts of processing. If this is correct, it should be possible to identify areas of the brain that map onto this theoretical distinction. Meta-analyses of fMRI and PET studies of emotion (Kober et al., 2008; F. C. Murphy, Nimmo-Smith, & Lawrence, 2003; Phan, Wager, Taylor, & Liberzon, 2002; Wager, Phan, Liberzon, & Taylor, 2003) are converging on a number of brain regions often involved in emotional processing, and some of these have been associated with each of the components of the modal model of emotion. Briefly summarizing these analyses, there is evidence of consistent involvement by traditional emotion areas such as the amygdala, insula, and striatum, which likely reflect them constituting a neural basis for the BAAS. The findings are less clear on the exact function of each of these regions and how they interact. A recent meta-analysis (Kober et al., 2008) attempted to address this by investigating the functional groupings of activations and the functional connectivity between these groups during emotional tasks. With regards to the BAAS, two closely related, yet distinct networks were identified; the core limbic group and the lateral paralimbic group respectively. The former is centred on the amygdala, along with hypothalamus, ventral striatum and pallidum, while the latter is centred on the insula and posterior orbitofrontal cortex (OFC), in addition to ventral striatum and hippocampus. Interpreting their findings the authors suggest that the core limbic group serves as an emotional integration and appraisal centre, receiving input from the thalamus directly without the involvement of traditional perceptual processing areas. The lateral paralimbic group was in turn interpreted as being central in the motivational aspect of emotion, i.e. effecting responses based on emotional appraisals. These networks were found to possess a high degree of functional connectivity, reflecting a strong tendency for them to be activated together during emotional processing. Thus, these findings, together with the findings from the other meta- analyses, indicate that these two groups together perform the functions of what the modal model refers to as the BAAS.

With regards to the BPAS, it is expected that this is subserved by the same areas of the brain that is involved in visual processing in general, i.e. the primary visual areas of the occipital cortex and associative areas in the parietal and temporal lobes. Kober et al. identified two networks in these areas, namely what they termed the medial posterior and occipital/visual association group. The former of these consists of the V1 of the occipital cortex and the posterior cingulate cortex, while the latter is composed of V4, V8, and MT+ area of the occipital cortex, in addition to the superior portion of the cerebellum. The authors interpreted their findings as reflecting the enhanced visual processing of affective stimuli, relative to neutral stimuli. Of note was that the authors found

significantly increased functional connectivity between BAAS areas and these visual areas, as is predicted by the modal model. This supports the contention that these areas constitute the core visual part of the BPAS, that, together with more general associative perceptual processing areas in the temporal and parietal lobes constitute the BPAS proper.

With regards to the temporal aspect of emotional appraisals, examinations of the structural connectivity of brain areas important for the generation of emotion (in particular the amygdala) has shown that there is a quick early warning visual circuit that feeds directly to these areas that circumvents traditional perceptual areas such as the occipital cortex (LeDoux, 2000). Evidence from neuroimaging supports this finding, and has shown that emotion related areas of the brain are in fact activated prior to activity in visual areas (Sabatinelli, Lang, Bradley, Costa, & Keil, 2009). These findings, seen in light of the modal model of emotion suggest a model of the temporal dynamics of emotion generation, starting with the early activation of the core limbic system that drives activity in both lateral paralimbic regions and BPAS areas. This is, however, likely to happen on a time scale below what is feasible to gauge using standard fMRI methods, leading to the prediction that these will be shown as co-activated in most experiments.

The precise nature of the dynamics of an extended emotional event has so far not received much attention in fMRI research. There are two reasons for this: First, studies have focused on establishing the constituents of emotion generation, rather than emotional experience proper. Second, they have almost exclusively induced emotions by way of static picture displays, that by their nature are seldom conducive to eliciting extended emotional events. To the author´s knowledge only one neuroimaging study of extended emotional events has been attempted hitherto (Koelsch, Fritz, v. Cramon, Müller, & Friederici, 2006). Using 1 minute pleasant and unpleasant music stimuli to induce emotion, this study found activity changes in response to both pleasant and unpleasant music in a number of core limbic and lateral paralimbic structures, including amygdala, insula, and ventral striatum. When looking at activation differences between the first 30 seconds and the remaining 30 seconds, activations of all of these structures were stronger during the late epoch of the emotional event. The authors interpreted this as being because the intensity of listeners' emotional experiences increased during the perception of both the pleasant and the unpleasant musical excerpts. This would be in accordance with the recursive aspect of emotion, as indicated by the modal model of emotion, though more research is needed to decide whether this is the case with emotions elicited by other means than music. This finding also supports our hypothesis that the physiological arousal seen in SE is driven by increasing conflict between emotional reactions and

top-down controlling influences.

In summary, the available evidence on what brain systems are involved in emotional processing dovetails with the modal model of emotion, and point towards amygdala, insula, striatum and posterior OFC being involved in core emotional processes such as primary emotional appraisal, implementing emotional responses and integrating these with ongoing processes. Thus, these areas are likely candidates for the BAAS system of the modal model of emotion. There is also evidence for there being a core emotion-related visual network, centred on primary visual areas in the occipital cortex These, together with general perceptual appraisal mechanisms related to the "high road" of processing, in parietal and temporal areas, are in turn likely candidates to constitute the BPAS proposed by the model.

3.2: The neural bases and temporal dynamics of cognitive reappraisal

As mentioned earlier, RE is thought to involve two separate systems, respectively the DBAS and OBAS. A series of fMRI studies are converging on the neural bases of these systems (Beauregard, Lévesque, & Bourgouin, 2001; Eippert et al., 2007a; Fowler, McCall, Chou, J. C. Holmes, & Hanenson, 1976; Lévesque et al., 2003; McRae et al., 2010; Ochsner, Bunge, Gross, & Gabrieli, 2002; Phan et al., 2005; Urry et al., 2006). Summarizing these findings Ochsner and Gross (2007, 2008) point to dorsal prefrontal cortex (PFC) and anterior cingulate cortex (ACC) regions as the likely neural bases for the DBAS. As the model predicts, the available evidence from structural connectivity studies in humans and primates indicates that this system does not possess extensive direct connections to candidate regions for the BAAS such as the amygdalae, insula and basal ganglia (Roberts et al., 2007). It is however extensively connected to the regions thought to implement the OBAS and BPAS (Roberts et al., 2007). The OBAS in turn is thought to be subserved by lateral and medial aspects of the OFC and ventral PFC as well as inferior aspects of ACC involved in representation of associations between emotionally relevant outcomes. Anatomical tracing studies have demonstrated strong reciprocal connections between the amygdala and insula and ACC, OFC, and ventrolateral prefrontal cortex (VLPFC) (Amaral & J. L. Price, 1984; Carmichael & J. L. Price, 1995; Ghashghaei & Barbas, 2002; Ghashghaei, Hilgetag, & Barbas, 2007; Mcdonald, Mascagni, & Guo, 1996). This means that the OBAS is ideally connected to afford regulatory influence on the BAAS, and, in turn, that DBAS regulation most likely is mediated by the OBAS.

Only one previous study has investigated the changes in functional connectivity associated

with reappraisal (Banks, K. T. Eddy, Angstadt, Nathan, & Phan, 2007). This fMRI study established that cognitive reappraisal of negative picture stimuli was associated with an increase in functional connectivity between the left amygdala and bilateral dorsolateral PFC, OFC, subgenual ACC, and DMPFC and inferior parietal cortex. That is to say that they found increased functional connectivity between candidate regions for the OBAS and the DBAS. They also found that increases in coupling between the amygdala, OFC and DMPFC were positively correlated with ratings of subjectively experienced negative affect. These findings were, however based on a the presentation of negatively valenced pictures in a blocked design. Because of this they were not able to investigate the temporal evolution of connectivity changes as a function of reappraisal, leaving open the question as to whether there are differing patterns in connectivity associated with different periods of an extended emotional event.

It is worth noting that our current knowledge about reappraisal is primarily based on the reappraisal of negatively valenced picture stimuli. As such there is little knowledge of the time-course of emotion regulation during a more ecologically valid extended emotional event. Only three studies have used stimuli conducive for such an investigation (i.e. film clips; Beauregard et al, 2001; Goldin et al., 2008; Levesque et al., 2004), and only one of these (Goldin et al., 2008) explicitly investigated the temporal dynamics of reappraisal. This fMRI study reported reappraisal related activity in frontal areas thought to implement the DBAS and OBAS, in addition to temporal, parietal and occipital areas thought to subserve the BPAS only in the early period (0-4.5 seconds) of their 15 second long film viewing task. They also reported a decrease of activity in primary emotional appraisal areas (bilateral amygdala and insula) in the late period (10.5-15 seconds) only. This finding indicates that RE activity follows the trajectory predicted by theory, in only showing increased activity during the early stages of an extended emotional events. Somewhat unexpectedly, however, it was found that decreased activity in BAAS areas only occurred after a considerable amount of time.

In contrast to the Goldin et al study, a series of ERP studies (Foti & Hajcak, 2008; Hajcak, Moser, & Simons, 2006; Hajcak & Nieuwenhuis, 2006; Macnamara, Foti, & Hajcak, 2009; Moser, Hajcak, Bukay, & Simons, 2006) indicate that the effects of RE are reflected in modulation of the late positive potential (LPP). The LPP is a midline ERP that becomes evident approximately 300 milliseconds following stimulus onset, and has a larger amplitude following the presentation of both pleasant and unpleasant compared to neutral pictures and words. As such the LPP appears to index the facilitated processing of emotional compared to neutral information (Hajcak, MacNamara, &

Olvet, 2010). The modulation of the LPP afforded by reappraisal has been reported to begin approximately 200 milliseconds after stimulus onset (Moser et al., 2006) thus showing a decrease of emotion-related activity earlier than what was reported by Goldin et al (2008).

Another ERP study (Gallo, Keil, McCulloch, Rockstroh, & Gollwitzer, 2009) showed that having the implementation intention (Gollwitzer & Sheeran, 2006) to perform RE in when exposed to negative stimuli results in reliable reductions of the P1 component. The P1 component reflects electro-cortical activity in higher level extrastriate areas of the visual cortex (Luck & Girelli, 1998) and is assessed in a time window around 100 ms after stimulus presentation. The component has been reported to discriminate between affective stimulus content, with high-arousing negative stimuli often eliciting larger P1 amplitudes (Carretie, Hinojosa, Martin-Loeches, Mercado, & Tapia, 2004) . Hence, reduction of the P1 by RE might reflect top- down influence on emotional visual processing rapidly after onset of stimulus. It might also reflect a direct influence on BAAS areas, since there was a high correlation between the scale of the reduction of experienced negative affect and the reduction of the P1. This finding, and those discussed above, indicate that reappraisal should show activity in the early epochs of an emotional event, in contrast with that reported by Goldin et al. (2008). However, the findings support the hypothesis that RE should show activity the earlier stages of an emotional event.

In summary, the available evidence indicates that RE is subserved by a number of regions involved in general cognitive control and executive function. The DBAS is likely subserved by regions of the dorsomedial PFC and cingulate cortex, while the OBAS is likely subserved by areas of the lateral and medial aspects of the OFC and ventral PFC as well as anterior portions of the cingulate cortex. With regards to the temporal aspect of RE, the evidence mainly accords with what is predicted by theory. Available evidence points to the DBAS and OBAS being activated in early portions of an extended emotional event, with concomitant increased connectivity between DBAS, OBAS and BAAS. These effects have been shown to correlate with decreased negative affect, and reduction of activity in BAAS areas. The exact time-frame of these changes is still open to debate, with some studies showing relatively immediate modulation of emotion-related activity, and others showing modulation only after a relatively long time period.

3.3: The neural bases and temporal dynamics of suppression.

The only study investigating the neural bases of ER through suppression is Goldin et al (2008). This fMRI study found that suppression of emotional expression resulted in increased

activity in the dorsomedial, dorsolateral and ventrolateral aspects of the PFC, as well as posterior temporal and inferior parietal activity. In particular, suppression produced significant responses in areas of right ventrolateral PFC previously related to inhibitory motor control (cf. M. Brass, Derrfuss, Forstmann, & von Cramon, 2005 for a review). This gives further credence to the contention that suppression is to be thought of as an instance of executive inhibitory control as described in our working model of SE, since these areas are often implicated in studies of inhibitory control using non-emotional experiments (Aron & Poldrack, 2005). With reference to our working model of SE, one possibility is therefore that we can parse these areas into areas related to the setting of the motor plan (reference state; dorsolateral PFC), areas effecting the motor inhibition (control; ventrolateral PFC) and areas monitoring the performance of the inhibition (comparator; dorsomedial PFC/ ACC).

There has been no explicit investigations of the time-course of SE by means of methods with high temporal resolution, such as ERP. The one study that explicitly has looked at activity over time during suppression is the aforementioned Goldin et al. (2008) study. This fMRI study found that SE had no discernible effects on brain activity relative to the unregulated condition before the late epoch of their film viewing task (10,5-15 seconds). This is in stark contrast to what one would expect looking at the literature from other behavioural inhibition tasks, which would predict an activation of several control- related regions following as little as 300 milliseconds post stimulus presentation (Chiu, A. Holmes, & Pizzagalli, 2008). This discrepancy can, to a degree, be explained by reference to our working model of SE. This predicts that SE induces conflict-related activity that increases with time. Thus, the activity observed by Goldin et al. is likely reflecting increasing conflict and activation of conflict monitoring and resolution areas rather than the initial activity related to implementing the strategy itself. Given the lack of early activity in areas involved in the Goldin et al. study, it might be that this implementation is reflected in changes in functional coupling between the expression driving BAAS areas and areas involved in the implementation of cognitive control. This hypothesis has yet to be tested, since there have been no studies of changes in functional connectivity as a function of suppression.

Summarizing, there has hitherto been little work done on the neural bases of SE. What available evidence there is indicates that SE is subserved by areas of the dorsomedial, dorsolateral and ventrolateral aspects of the PFC, as well as posterior temporal and inferior parietal areas. Hitherto, SE has only been shown to have distinct effects on neural activity in the late stages of an extended emotional event. It is possible, however, that this activity reflects general conflict-

monitoring and -resolution related processes rather than activity related to the implementation of SE in particular.

4: Implications and predictions for the current study

The current study aims at comparing changes in neural activity and functional connectivity measured by fMRI as a function of emotion regulation strategy employed. The strategies of reappraisal and suppression were chosen because they are examples of a commonly employed, respectively, antecedent and response-focused ER strategy. Given their different focus, it is predicted that they will have differing time-courses, and activation and connectivity patterns, as has been discussed above. Based on the models proposed above and previous studies on the neural foundations of emotion and ER, it is possible to garner some hypotheses about what these differences are, and how they relate to the current study. These predictions will be formulated below with hypotheses about effects of each strategy on experienced negative affect, neural activity, time course and connectivity discussed separately, for ease of presentation. To avoid difficulties involved with interpretation of reductions of BOLD signal and decreases in connectivity, these hypotheses will be formulated in terms of increases in activity relative to the unregulated emotional event.

4.1: Predictions for the core processes of suppression and reappraisal

First, with regards to effects of ER on subjectively experienced affect, it is expected that both strategies will result in some reduction of experienced affect. RE will likely be superior to SE in reducing subjectively experienced negative affect, due to the fact that it actively modulates emotional appraisal areas. Hence, for RE these effects are predicted to be correlated with relatively less activity in the BAAS, while SE is predicted to have no differential effects on BAAS activity.

Second, with regards to the areas involved in the implementation of each strategy, it is expected that in the RE condition will activate areas involved in verbalization and cognitive control (the DBAS) in addition to modulation of areas of involved in perceptual appraisal (the BPAS) and contextualising of emotion (the OBAS). In contrast, the implementation of SE will result in increased activity in conflict monitoring, response inhibition and cognitive control areas.

Third, with regards to the time course of activity, the modal model of emotion, the process model of emotion regulation and earlier work using fMRI, all predict that RE effects will be evident in exclusively in relatively early epochs of the emotional event. Earlier empirical work predicts that this will be concomitant with decreases in BAAS activity later in the event. For SE it is expected

that the strategy will induce a cognitive conflict, which is reflected in increased activity in areas involved in conflict monitoring and response inhibition. It is anticipated that this activity will increase over time, as each concurrent emotion-generation cycle amplifies the induced cognitive conflict by reengaging the BAAS. It is therefore expected that activity in later epochs will increasingly reflect the engagement of systems related to conflict monitoring.

Fourth, with regards to changes in connectivity, it is expected that these will track activation patterns to a large degree, but will show some unique effects. RE is likely to be accompanied by increased connectivity between BAAS areas and areas subserving the OBAS and BPAS in early epochs. In contrast, SE is likely to be accompanied by increased connectivity between BAAS and conflict-monitoring and response modulation, and this is likely to increase with time.

4.2: The current study: Outline of the experiment

The results presented in this thesis is the first instalment of a larger study, the goal of which is to establish a unified causal model of the neural network underlying emotion regulation in a normal population using the methodological framework of SCAN. A first step towards establishing this model is investigating the temporal dynamics of neural activity within and functional connectivity changes between brain areas associated with different ER strategies. The current study aimed at achieving this through measuring the neural responses related to regulation of subjectively experienced disgust and the expression of disgust using fMRI. The emotion of disgust was chosen because it is both one of the basic emotions (Matsumoto & Ekman, 2009), and an emotion that shows great cultural and individual variability (Rozin, Haidt, & McCauley, 2008) and thus gives precedence to neither of the traditional accounts of emotion. It is also an emotion that can be induced in such manner that it becomes an extended emotional event, which is required if one is to investigate the temporal dynamics of the networks involved. In the current study, this was achieved by using film clips of disgusting events. The two strategies examined in this study were chosen on the basis of them being thoroughly documented, and because there has yet to be any direct attempt at establishing an empirical model of them as dynamic systems. The purpose of this study is to lay the groundwork for this, by investigating the neural architecture and temporal dynamics of each strategy using neuroanatomically specific and temporally sensitive analysis methods. fMRI allows for a spatially exact measurement of the mesoscale (temporal resolution of seconds) temporal dynamics of emotion regulation. This allowed the current study to assess changes in brain activity and functional connectivity as a function of the two ER strategies during early, middle and late epochs of the emotional event. The ultimate goal of the study is to map the temporal dynamics of

activity and connectivity changes during RE and SE, and combine these with the working models to establish empirical models of the activity and connectivity changes that characterize each strategy.

4.3: The current study: Central hypotheses

The main hypothesis of this study is that the effects of SE and RE will have different effects on subjectively experienced affect. These effects are expected to have neural correlates with regards to 1) areas involved in implementing the strategy that show signature changes in 2) neural dynamics and connectivity changes over time that are particular to that strategy and lead to 3) effects on areas of the brain involved in emotional processing.

A number of subsidiary hypotheses based on the predictions made above guided the analysis. First, unregulated emotional events relative to neutral events were predicted to result in widespread activity in BPAS areas such as occipital, temporal and parietal cortices. More importantly activation was predicted in one or more of the above discussed candidate regions for the BAAS, in particular the amygdala and/or insula.

With regards to differing effects of the emotion regulation strategies it was predicted that 1) RE would be superior to SE in reducing negative affect, but that 2) SE also would result in reduced negative affect relative to the unregulated condition.

RE was predicted to 1) elicit activity in superior frontal areas subserving the DBAS and inferior frontal areas, subserving the OBAS, as well as temporal, parietal and occipital areas subserving the BPAS. 2) The activity of DBAS, OBAS and BPAS will be evident in early periods of the film, with 3) decreased activity in the BAAS in later periods. 4) Connectivity between the BAAS and OBAS will increase in early periods, while connectivity to BPAS will increase in later periods.

SE was predicted to 1) elicit activity in frontal areas involved in motor control, executive control and response inhibition, as well as areas involved in conflict-monitoring. Based on earlier work, it was predicted that 2) this activity will be largely apparent in late periods of the emotional event with 3) no decreased activity in BAAS. It was also predicted that 4) SE will result in the BAAS being increasingly coupled with control and conflict monitoring areas as a function of time.

5: Materials and methods

5.1: Film stimuli validation

Part of the current study consisted of the development of a film stimulus set that would reliably induce disgust in subjects. As such, 10 subjects rated 92 disgust inducing negative and 53 neutral 15 second film clips on a 600 point Visual Analog Scale (VAS), on which 0 was extremely negative, 300 neutral and 600 extremely positive. Included in the set of films was the 40 film clips that served as stimulus material in the Goldin et al. (2008) study. The bipolar valence scale was chosen instead of a monopolar scale ranging from neutral to negative, in order to I) ascertain the de facto neutrality of the stimuli, as opposed to them being positively valenced and II) to avoid biasing the ratings in the direction of negativity. The film clips were presented in random order using the E-Prime stimulus presentation software on a 13" LCD screen.

A subset of 34 film clips with the most consistently high negative affect ratings combined with the lowest standard deviation, were selected for use in the fMRI- experiment and pre-experiment training session. In addition a total of 12 neutral film clips, matched to the stimulus properties of the negative stimuli, were selected on the basis of rated neutrality and low standard deviations. A post hoc t-test showed a significantly greater ratings of negative affect for the negative (μ = 175.75, SD = 17.23) vs neutral (μ= 324.31; SD = 27.97) film sets; t(46)= -21.63, p<0.001.

5.2: Participants

39 healthy subjects, all with Norwegian as native language, volunteered to participate in the experiment. All subjects had normal or corrected-to-normal vision, no reported neurological or psychiatric history and no structural brain abnormality. (Mean age: 26.8, range 19-31, 23 female). Prior to scanning all subjects filled out an informed consent form, an MR- compatibility checklist, and Norwegian translations of the Big Five Personality Inventory, Emotion Regulation Questionnaire, and Positive and Negative Affect Schedule. After scanning the subjects underwent a neuropsychological assessment using the WASI test battery as well as the D-KEFS Stroop task. Results from these measures will not be presented in the current paper, to facilitate clarity of presentation.

5.3: Prescan training procedure

Prior to magnetic resonance imaging (MRI), participants were trained in specific reappraisal and suppression strategies while viewing 6 practice films and being trained on the experimental

setup. Reappraisal instructions encouraged thinking objectively to decrease emotional reactivity to films, for example, by assuming the perspective of a medical professional watching an instructional video, inventing positive reinterpretations of negative stimuli, or actively thinking of the film as being fraudulent (such as a horror movie). Subjects were debriefed after each film clip and given feedback on the appropriateness of their chosen strategy. Suppression instructions focused on training participants to keep their face still while viewing films so that someone watching their face would not be able to detect what was being experienced subjectively. Watch instructions were to respond to the stimuli in a natural way. As a final check that the subjects understood the task, subjects were asked to describe, in their own words, how they would follow each instruction just prior to entering the scanner.

5.4: Experimental Task

The experiment was two counterbalanced orders of the 40 film stimuli that matched negative films with the different instructions to reappraise, suppress, or watch that were pseudo-randomized to ensure no more than two consecutive repetitions of the same condition (see Figure 5). The task consisted of four conditions: 10 watch-neutral, 10 watch-negative, 10 Reappraise, and 10 Suppression trials. Each trial consisted of: 1) 3 sec instruction ("Watch," "Think objectively," "Keep face still"); 2) 15 sec film; 3) two consecutive 6 sec "How do you feel?" ratings on a 600 point VAS where 0 = extremely negative, 300 = neutral, and 600 = extremely positive; 4) a 3 second instruction to judge the symmetry of the following picture; 5) an 8 second presentation of a scrambled picture; and 6) a final 6 second rating of subjective affect. There were no order effects evident on negative emotion ratings or blood oxygenation level-dependent (BOLD) responses.

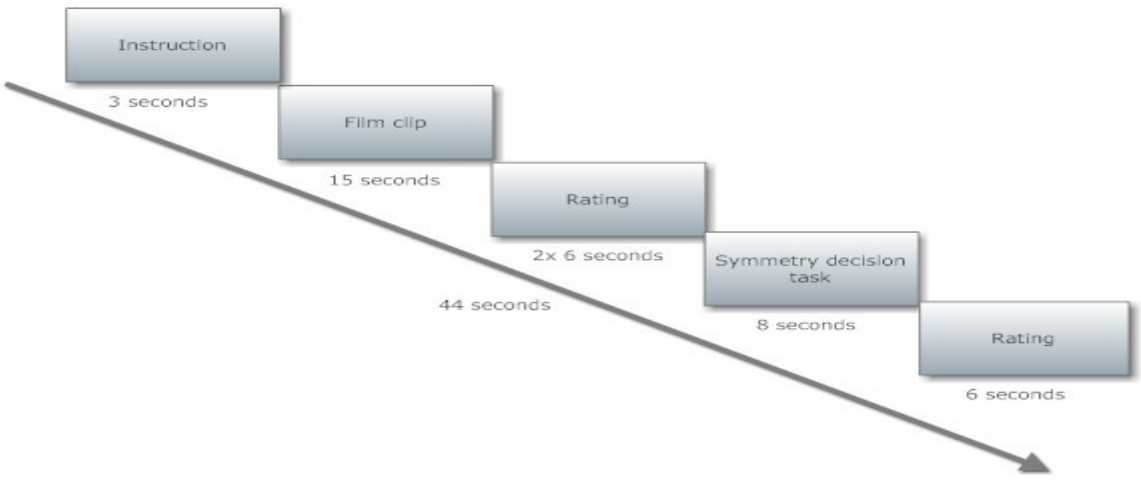


Figure 5. Experimental design for a single trial

This design is based on the design used in the Goldin et al. (2008), but differs in two respects. First, the task employed a more extensive rating procedure, meant to a) sample subjectively experienced affect in more detail than done before, b) gauging subjectively experienced affect on a bipolar, rather than unipolar scale, and c) serve as a check of the efficacy of the distraction task. Second, the design employs a challenging active distraction task (point 4-5) as opposed to the passive viewing task used by the previous study. This is meant to facilitate a return to baseline after each trial since active and cognitively demanding tasks have been shown to be more effective at this than passive tasks.

5.5: Data Acquisition

Neural measurements were performed with a Philips Achieva 3-T whole-body magnetic resonance unit equipped with an eight-channel Philips SENSE head coil (Philips Medical Systems, Best, the Netherlands). Images were acquired with an 8-channel Philips SENSE head coil. Functional images were acquired using a BOLD- sensitive T2*-weighted echo-planar imaging (EPI) sensitivity encoded single-shot echo-planar sequence (SENSE; Pruessmann, Weiger, Scheidegger, & Boesiger, 1999). The following acquisition parameters were used: echo time = 30 msec, repetition time = 2250 msec θ = 78°, field of view = 22,4 cm, acquisition matrix = 112 × 112, voxel size: 2 × 2 × 2 mm, with a 0.75mm slice gap. SENSE acceleration factor *R* = 2.3. Using a midsagittal scout image, 36 interleaved axial slices were placed along the anterior–posterior commissure (AC-PC) plane covering the entire brain with the exception of the inferior portions of the cerebellum.The first 5 volumes from each run were automatically discarded to allow for T1 equilibriation effects.

In addition anatomical T1-weighted images were obtained using a turbo field echo (TFE) pulse sequence with TR of 9,64 ms, TE of 4,59 ms and a flip angle of 8°. This full-brain structural volume consisted of 192 sagitally oriented slices with a voxel size of 0.97x0.97x1 mm. The field of view measured 256x256 mm. The slices of the structural volume were placed along the AC-PC line. Finally, a gradient-recalled sequence was applied to acquire two complex images with different echo times (TE = 3.5ms and 6.1 ms respectively) that would later be used to generate B0 field maps for use in preprocessing.

The film clips were presented through a pair of head-coil mounted NNL Visual System binoculars (NordicNeuroLab AS, Norway), with a screen resolution of 800x600 pixels. Presentation

of stimuli and ratings of subjective feeling after each trial were recorded using E-Prime software (Psychological Software Tools, Inc., Pittsburgh, Pennsylvania), and an MR- compatible joystick.

5.6: Preprocessing

5.6.1: Realignment and unwarping

All preprocessing was performed using SPM8. EPI time series were corrected for motion and distortion using Realign and Unwarp (Andersson, Hutton, Ashburner, Turner, & Friston, 2001) together with the FieldMap toolbox (Hutton et al., 2002) in SPM8. This procedure consisted of first using the B0 maps to calculate a Voxel Displacement Map (VDM) for each subject, using the Fieldmap toolbox. The functional images were then realigned and unwarped, using the VDMs to correct for distortions induced by both movement and scanner susceptibility artifacts. At this point 3 subjects were removed from further analysis due to excessive movement (>3mm linear displacement, or >3 degrees rotation) .

5.6.2: Coregistration

To ensure optimal coregistration of functional and structural images, the T1 weighted images were segmented prior to coregistration using the Segment function of SPM. The resulting grey matter, white matter and bias-corrected images were then combined to create a skull-stripped structural image, that was subsequently coregistered to the functional images. The original structural image was then coregistered to the skull-stripped image.

5.6.3: DARTEL normalisation and smoothing procedure

The T1 images were then segmented using the 'New Segment' routine in SPM8 to create DARTEL imported white and grey matter images. Using the DARTEL Toolbox (Ashburner, 2007), the group mean structural template as well as individual flow fields from subject space to DARTEL group mean space were calculated. These flow fields and the DARTEL group template were in turn used with the improved unified normalization and smoothing routine in the DARTEL toolbox to warp the beta images to the MNI template. Following the recommendations of Strother et al. (2004) the data was smoothed using a Gaussian kernel set at 5x5x7mm full width half maximum (FWHM), and the images were resampled to 2x2x2.75 mm. The purpose of using this comparatively small smoothing kernel was to strike a balance between statistical strength and anatomical specificity, with a slight bias in favor of specificity.

Contrary to the standard preprocessing pipeline in the SPM- framework, fixed effects analyses were performed on unsmoothed and unnormalised functional data (see Analysis section). The resulting beta-estimate images were then normalised and smoothed using the DARTEL toolbox in SPM8. This was done to avoid inadvertent smoothing of the functional images as a consequence of interpolation and resampling (Strother et al., 2004). Using this procedure it was possible to reduce unwanted smoothing due to interpolation to a single procedure (i.e. the Realign and Unwarp step), as opposed to the two or more steps requiring interpolation in the standard SPM preprocessing stream.

6: Analysis

6.1: Subject level analysis

Statistical analysis was initially performed at a fixed effects single subject level based on the General Linear Model in SPM8 (Friston et al., 1994) on unsmoothed, realigned and unwarped (see Preprocessing section) functional data in subject space. Low-frequency drifts were removed using a temporal high-pass filter (cut-off, 143s). To account for extraneous variance each trial was modelled *in toto*, with separate regressors for Instruction, 3x Rating, and Wash. Following earlier work by Goldin et al. (2008) three event regressors were specified for each of the emotion regulation strategies, allowing differentation between activity during the Early (0-5), Middle (5-10), and Late (10-15) parts of each trial. The negative-watch and neutral-watch were modelled as single regressors, again in accordance with Goldin et al. (2008).

Design matrices were generated by convolving these regressors with a canonical hemodynamic response function and its temporal and dispersion derivatives (Friston et al., 1998). The motivation for including these two derivatives was to reduce the impact of spatially varying hemodynamic delays and extents (i.e. phase shifts) due to stimulus properties, individual differences in strategy implementation, and/or slice timing differences that would result in latency-induced amplitude biases. The effects modeled by the derivative terms are interpreted as a shift of the hemodynamic model in time and dispersion . It has been shown that the hemodynamic response function plus temporal derivative produces the most sensitive analyses for event-related fMRI analyses (Hopfinger, Büchel, A. Holmes, & Friston, 2000). This is because adding the derivatives to the model allows one to address delay-induced modeling mismatches, and thus reduce the variance going into the error term of the model. However, including these derivatives runs the risk of introducing an amplitude bias induced by a delay difference between the hemodynamic model and

the data (Calhoun, Stevens, Pearlson, & Kiehl, 2004). This amplitude bias is due to the use of only the nonderivative portion of the model in testing for significant amplitudes. To alleviate this potential problem the true amplitude of the hemodynamic response (a function of both the non-derivative and derivative terms) was estimated by applying the method proposed by Calhoun et al. (2004) to integrate each canonical HRF and its temporal derivative using a customized MATLAB script. The dispersion derivative has not been established suffer from the same bias-inducing difficulties, and was therefore not included in the final bias-corrected beta-estimate images, but was still included to facilitate further reduction of the error term. The bias corrected beta-images were then normalized and smoothed using the DARTEL normalise to MNI function as described above. Finally, a series of linear subtractions were performed to create T-test contrast images for each effect of interest, that were subsequently passed on to the group level analysis.

6.2: Group level analysis

The second level random-effects analysis was performed using robust regression, a technique that both increases statistical power and decreases false positive rates in the presence of outliers (Wager, Keller, Lacey, & Jonides, 2005). The reason for using this method of analysis rather than a standard SPM RFX model was to allow for the inclusion of subject's report of subjective experience as an index of i)ER success and ii)emotional reactivity. This index was calculated for each subject as the average difference in negative affect reports by for the conditions i) [Reappraise - Watch-negative] , ii) [Suppress - Watch-negative], and iii) [Watch-neutral - Watch-negative]. The 7 second-level design matrixes (3*RE + 3*SE+1*Watch) included two regressors: one corresponding to ER success or emotional reactivity, and the other an intercept term. ER success scores were centered by subtracting the mean, allowing the intercept term to be interpreted as the population estimate for ER-induced activation [ER > Watch] for a subject who shows average success at ER for each strategy. Thus, the interpretation of the success and reactivity regressors is the change in ER-induced activation as a function of success, i.e. the activation- ER success relationship. The advantage of including ER-success induced activation in the model is that it accounts for known sources of individual variation when testing the significance of average activation contrast values. Thus, for voxels that do show a brain activity-reappraisal success relationship, this model has greater sensitivity to detect overall activation compared with an intercept-only model (which is what is typically performed, e.g. in SPM and FSL). Finally an explicit brain mask based on an optimally thresholded normalised mask (Ridgway et al., 2009) of the first level brain masks was applied to account for peripheral distortions in the contrast images as a consequence of the DARTEL normalisation algorithm.

Due to the comparatively small amount of smoothing induced in preprocessing, the asymptotic formula underlying SPM´s native multiple comparison correction methods (i.e. False Discovery Rate (FDR) & Family Wise Error (FWE)) reduces the accuracy of the cluster p-value estimates of these methods. This follows from the fact that they are based on Random Field Theory (RFT) which is valid only if the data in question approximates a smooth, Gaussian sphere. Therefore an alternate, simulation based, approach to correcting for multiple comparisons was employed, by using the Monte Carlo simulation method AlphaSim implemented in the AFNI library (Medical College of Wisconsin). This takes into account both family-wise error, extent thresholds and smoothness estimates in the same way as, e.g. the topological FDR correction of SPM8, but without relying on the assumptions of RFT. AlphaSim does this by taking into account the voxelwise and the cluster–volume thresholds to establish a clusterwise *p* value that protects against false-positive detection of activation clusters at a given value α (Forman et al., 1995). For the whole-brain block analysis (Watch- Negative vs. Watch- Neutral), the cluster extent threshold *k* was set at >31 contiguous voxels with a voxel threshold of $p < .001$ to protect against false-positives at a rate at $\alpha < 0.05$ overall. Because there were more time points per 15 sec block in the contrast of watch-negative versus watch-neutral conditions compared with the component analyses, there was less power in the component analyses compared to the block analyses. For this reason, a slightly less stringent joint-probability cluster threshold ($p = <.005$ & $k => 50$) was used for the component analyses ($\alpha = <0.1$) than for the block contrast analyses ($\alpha = <0.05$).

The neuroanatomical location of individual activation maxima and submaxima was established using the probabilistic cytoarchitectonic maps included in SPM Anatomy toolbox (Eickhoff et al., 2005). This toolbox was also used to calculate the percent signal change related to each of the experimental regressors for each subject.

Several conjunction analyses were performed using an SPM of the minimum t-statistic over individual contrasts (Friston, A. Holmes, C. Price, Büchel, & Worsley, 1999). The conjunction procedure is performed using the framework described in Friston et al. (Friston, Penny, & Glaser, 2005), as suggested by Nichols et al. (Nichols, Brett, Andersson, Wager, & Poline, 2005), testing the conjunction null hypothesis that there is only *n*-1 effects (i.e. contrasts) that are positive in the conjunction. For the conjunction analyses reported the conjunction threshold was calculated based on a derivation from equation 3 in Friston et al. (1999), yielding the formula $\gamma c = \alpha c^{1/n}$ where γc is the conjunction uncorrected false positive rate (FPR), αc is the uncorrected FPR for each contrast

tested, and n is the number of contrasts included in the conjunction. γc was set at .0001, uncorrected, for all conjunction analyses, unless otherwise noted. The extent threshold was arbitrarily (since the null distribution for minimum field statistics has not been derived) set at *k*>50.

6.3: PPI analysis

To assess changes in functional connectivity of BAAS regions as a function of ER strategy, the current analysis carried out an examination of Psychophysiological Interactions (PPI; Friston et al., 1997; Gitelman, Penny, Ashburner, & Friston, 2003) which is intended to capture interactions between brain regions in relation to the experimental design. A PPI analysis is used to compare the functional 'coupling' of different brain regions (physical component) during different tasks (psychological component). This allows the PPI analysis to capture the modulation of activity in one brain region or volume of interest (VOI) by activity in another brain region dependent on specific active tasks. As such, the PPI analysis examines differences in functional connectivity between regions, i.e. the contextually dependent influence of one region on another as a function of task manipulation. In the analysis of neuroimaging time-series functional connectivity is defined as the temporal correlations between spatially remote neurophysiological events (Friston, 1994). This means that an observed significant PPI effect would demonstrate that inter-regional coactivation was significantly greater during the implementation of emotion regulation tasks, than during the passive viewing task. Of note, because it is a correlational analysis, a significant PPI does not inform us about the directional nature of the regression slope under each condition individually, it only shows the direction of the change in covariation (increase or decrease) between the tasks (Friston et al., 1997).

6.3.1: VOI definition

The purpose of the PPI analysis in this study was to examine changes in the connectivity of bottom- up emotional appraisal systems as function of emotion regulation strategy. Given the established correlation between the experience of disgust and the insula, this area was chosen as an *a priori* source region of interest. The current analysis was directed at examining differences in connectivity between ER and Watch tasks in relation to insula responses to negative films, and not necessarily changes specific to insula responses modulated by ER. To achieve this a 2nd level Repeated Measures ANOVA was used to perform the global conjunction analysis of [Reappraise > Neutral AND Suppress> Neutral AND Watch>Neutral], which revealed a bilateral activation cluster in the anterior insula at FWE corrected for multiple comparisons at α=<0.05 (MNI coordinates left; 42 20 2, 23 voxels; right; -40 16 0, 31 voxels). By using a conjunction analysis instead of singling

out voxels deactivated by the respective ER strategies, the time series extracted reflect voxels that exhibit increases in signal as a function of digust- inducing stimuli in general, and a such are more likely to reflect general emotion related functioning. This avoids biasing the connectivity analysis towards finding an [ER>Watch] connectivity pattern, something a more conventional approach based on finding voxels exhibiting negative BOLD responses to ER strategies might do.

6.3.2: VOI extraction and PPI analysis

The significance for the VOI extraction was set to $p = .005$ (uncorrected) with more than 5 neighboring voxels. The VOI was individually defined through a two step procedure: First the point in subject space corresponding to the peak voxel of the group activation was determined by applying a deformation composed of a) the inverse warp of the affine registration from DARTEL space to MNI space used in the normalisation procedure and b) the inverse of the flow field from subject space to DARTEL space. A 10 mm radius sphere ROI was centered on this point, which served as a restriction on the search volume for activation corresponding to the group activation. This was defined as the peak maxima closest to the coordinates of the subject space transformed coordinate of the group maxima (i.e. the center of the search volume). The local maxima in subject space was used for extracting the time series of that voxel and the 10 mm spherical region surrounding it, forming the VOI used as a seed region in the PPI analysis. This procedure allowed for individual differences in functional anatomy to be accounted for, without losing the specificity allowed for by the 2nd level conjunction analysis. 2 participants has to be excluded from further analysis because they did not show a significant activation within in the search volume, leaving a total of 34 subjects in the final PPI analysis.

The time-series data of the first eigenvariate of the VOI was corrected for an effects of interest F-contrast. Then one vector containing the main effect of the contrasts of interest (P regressor, psychological variable, i.e. task type), a second vector representing the VOI time-course (*Y* regressor, physiological variable, i.e. measured BOLD signal), and a third vector contrasting the time-series of the estimated neural response for the conditions of interest (PPI regressor, interaction of the psychological and physiological variable) were generated. The PPI analysis convolves those regressors with the canonical hemodynamic response function to estimate the effects of the regressors. Brain sites evincing contextual coupling with the insula that were stronger during the ER conditions compared to the Watch-negative condition were determined by a one tailed *t*-test at the first level.

Applying the same procedure as earlier described for the BOLD whole-brain analysis, the group level, random effects analysis was performed using robust regression, forming 6 design matrixes (3 time periods * 2 strategies) with separate regressors specified for ER success and the other an intercept term. The interpretation of the intercept term is here the population estimate of functional coupling increases between the seed region and other brain regions for an individual showing average success at ER. The same joint-probability cluster threshold ((p =<.005 & k=> 50) = α =<0.1) was used as for the whole brain component analyses.

6.4: Analysis strategy

To test the main and subsidiary hypothese a multi-level analysis strategy was used. First, whole-brain activation and connectivity maps for each [Strategy(RE,SE)*Time(Early, Middle, Late)]>Watch-Negative contrast was created. This contrast group examines activity and connectivity changes that was related to each strategy, controlling for emotion-related effects. If one of these basic contrasts showed significant activation, they were passed to the next level. For each strategy, direct comparisons were then performed between each time period showing significant activity in the previous analysis. Then, to assess the regulatory effects of each strategy, percent signal change (PSC) was extracted from BAAS areas identified in the [Negative>Neutral] contrast. Conjunction analyses were performed to identify effects common to contrasts showing significance earlier. This analysis examines whether there is a general effect of strategy that was consistent over time, controlling for emotion-related effects and time-period specific effects. Finally, disjunctive analyses were performed, that examines whether there are specific effects in each time period, controlling for general strategy and emotion-related effects.

Direct comparisons between the strategies were then performed in each time period either of them had basic contrasts showing significant effects. First a conjunction analysis was performed for each strategies, over all significant time periods. This analysis examines whether there are general emotion-regulation related effects, while controlling for emotion-related effects and strategy specific effects. Finally, disjunctive analyses were perfomed, that examines whether there are specific effects of each strategy in each time period, controlling for general emotion regulation and emotion-related effects.

7: Results

7.1: Behavioural results

7.1.1: Emotion induction

Mean ratings of affect for each condition is shown in Figure 6. To ascertain whether or not the negative film stimuli were successful in eliciting subjective negative emotion, a paired samples T-test was performed on the mean of the first two rating sessions of the negative and neutral conditions, respectively. There was a significant difference in the scores for the negative- watch (μ= -35.70, SD= 60.93) and the neutral- watch (μ=32.30 , SD= 48) conditions; t(36)=-7.93, p= <0.005.

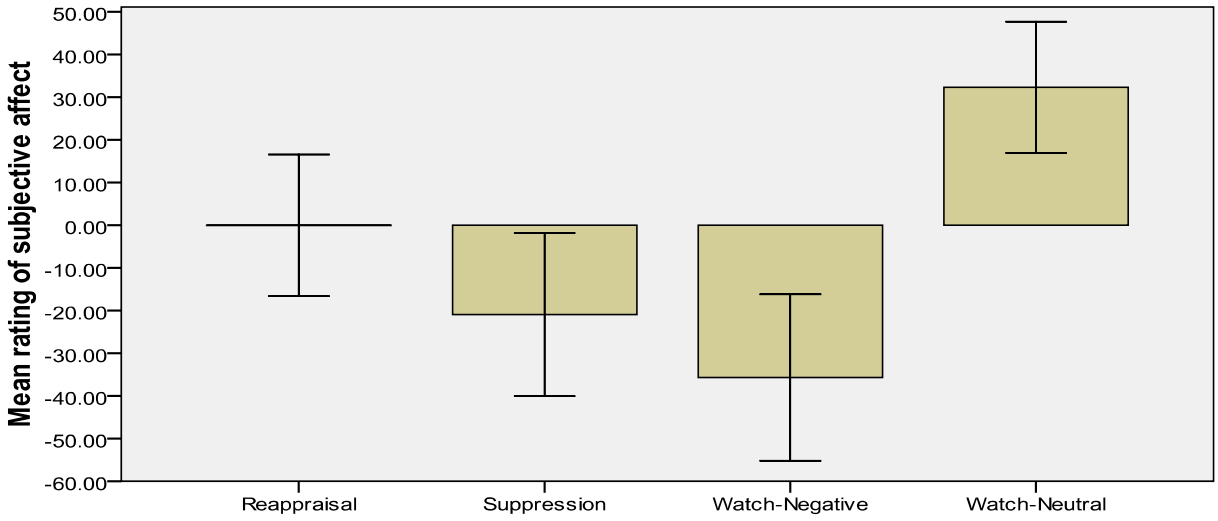


Figure 6. Mean rating of affect for each of the experimental conditions on a 600 point VAS-scale where 0 = neutral, 300 = extremely positive and -300 = extremely negative. Error bars= +/- 2 SEM.

7.1.2: Emotion regulation efficacy

To investigate the primary hypotheses that the respective emotion regulation strategies would have different effects on experienced affect, paired samples T-tests was performed on the mean of the first two rating sessions of the Reappraise and Suppression conditions versus the Watch-Negative condition. There was a significant difference in the scores for the Reappraisal (μ= -0.02, SD= 51.80) and the Watch-Negative (μ= -35.70, SD= 60.93) conditions; t(36)=7.35, p= <0.005. There was a smaller, but still significant, difference in the scores for the Suppression (μ= -20.92, SD = 59.71) and the Watch-Negative (μ= -35.70, SD= 60.93) conditions; t(36)= 3.98, p= <0.001. Direct comparison of the two emotion regulation strategies showed that there was a significant difference in the scores for the Reappraisal (μ= -0.02, SD= 51.80) and the Suppression (μ= -20.92, SD = 59.71) conditions; t(36)=4.43, p= <0.005.

7.2: fMRI results

7.2.1: Emotion induction check

The [Watch-Negative> Watch- Neutral] contrast serves as a check of succesful emotion induction by the negative stimuli (results presented in Appendix: Table 1; figure 7). In accordance with predictions and earlier findings extensive activations were found in occipital, parietal, temporal, frontal and subcortical areas.

7.2.2: Emotion regulation results

To test for hypothesized differential ER effects on neural activity and connectivity as a function of time, each of the components of the ER strategies (Early, Middle, Late) were contrasted against the Watch-Negative condition. Then, to assess the regulatory effects of each strategy, percent signal change (PSC) was extracted from the bottom-up emotional appraisal areas (i.e. bilateral insula) identified in the [Negative>Neutral] contrast.

7.2.3: Reappraisal results

7.2.3.1: Reappraisal related activations

The [Reappraisal>Negative-Watch] contrast allows one to identify brain regions preferentially activated during ER through reappraisal during each time period. Results showed enhanced responses in a number of primarily left lateralized brain areas in the Early (0-5 second) and Late (10-15 second) time periods (see Appendix: Table 2; Figure 7). In the Early period activity was observed in candidate DBAS (left Inferior Frontal Gyrus (IFG), p. Triangularis, left Superior Medial Gyrus (SMG) and Superior Frontal Gyrus (SF)), OBAS (left IFG, p. Orbitalis), and BPAS (bilateral lingual gyrus, left mid-occipital gyrus, left middle temporal gyrus (MTG) and temporal pole, left inferior parietal cortex (IPC)) areas. In the Late period activity was seen in mainly the same areas, with the addition of bilateral caudate nucleus activity, a candidate BAAS area.

To investigate overlap between time periods, direct comparison of the Early and Late periods contrasted against the negative-watch condition were performed by two-sample t-tests using SPM (see Appendix: Table 3). Conjunction analysis revealed clusters in the left IFG (p. triangularis and p. orbitalis; MNI: -51, 25, 0; 278 voxels, peak T value: 3.92) Superior Medial Gyrus/SFG (MNI: -14, 62, 30: 129 voxels, peak T value: 3.34), left MTG (MNI: -56, -32, -3, 109 voxels, peak T value: 2.89) and left pre-SMA (MNI: -6, 12, 69, 67 voxels, peak T value: 2.69). The Early>Late

contrast revealed relatively more activity in candidate areas for the BPAS (bilateral lingual gyrus, calcarine gyrus and fusiform gyrus, inferior temporal gyrus), and DBAS (bilateral middle cingulate cortex (MCC), left SFG and right IFG, p. Opercularis) and right thalamus. The Late>Early contrast revealed increased activity in candidate DBAS (right SFG and SMG), and BAAS (right putamen) areas.

To test our third hypothesis that decreased activity of the BAAS will be evident only in late areas, paired samples T-tests performed on PSC in the right and left insula in the Early, Middle and Late periods compared to the Watch- Negative condition. The results showed that there was a reduced emotion-related neural signal during the bilaterally during the early (left insula; $t=2.15$, $p<0.05$; right insula; $t= 2.89$, $p<0.01$) and in the right insula during the late period ($t=2.13$, $p<0.05$) with a trend towards significance for the left insula ($t=1.86$, $p=0.07$). To examine this further a paired sample T-test was performed comparing PSC in the Early and Late periods exclusively. This revealed that there was no significant difference in PSC between the Early and Late periods for the right insula($p= .23$), nor the left insula ($p= .30$).

7.2.3.2: Reappraisal related connectivity increases

PPI analyses were performed independently for the left and right insula VOIs, to test our fourth hypothesis that connectivity will increase between BAAS and OBAS during the early period, and BAAS and BPAS during the late period (results shown in Appendix: Table 4; figure 8). The analyses showed that activity in the left insula was accompanied by task-dependent (Reappraise>Watch) functional interaction with specific areas in each of the time periods. In the Early (0-5 seconds) and Middle (5-10 seconds) periods there was an increased functional coupling between the left insula and candidate OBAS areas (IFG, p. Orbitalis). In the Late (10-15) period there was a change of coupling between the left insula and candidate DBAS areas (IFG, p. Triangularis, Superior Medial Gyrus). Analyses using the right insula as seed region (see Appendix: Table 4; Figure 8), showed changes in functional connectivity only in the Early and Middle periods. In the Early period there was an increase of functional coupling with the candidate BPAS areas (precuneus and angular gyrus). In the middle period functional connectivity increased with both candidate BPAS (Superior Temporal Gyrus) and DBAS (pre- SMA) areas.

Direct comparison (results reported in Appendix: Table 5) of the time periods was done by way of a one way repeated measures ANOVA using SPM for each insula seed separately. To investigate similarities between the time periods a conjunction analysis over all time periods was

performed. For the left insula seed, this revealed a significant cluster in the left middle orbital gyrus and IFG, p. Orbitalis (MNI: -34, 44, -12, 89 voxels, peak T value: 2.36) and left middle frontal gyrus (MNI: -34, 26, 45, 62 voxels, peak T value: 2.00). Direct contrasts of the individual time periods against the mean of other two revealed no unique effects for the Early period. The Middle period showed unique increased connectivity to candidate DBAS (right SFG), OBAS (left IFG, p. Orbitalis) and BPAS (right hippocampus/parahippocampus) areas, in addition to the right anterior insula. The Late period showed unique increased connectivity to candidate DBAS (left MFG and IFG, p. Triangularis), OBAS(left superior orbital gyrus) areas and BAAS areas (left putamen and left posterior caudate nucleus) and left thalamus.

For the right insula seed, conjunction analysis revealed clusters in the left MTG (MNI: -62, 14, -8, 240 voxels, peak T value: 2.36), left midorbital gyrus (MNI: -1, 52, -14, 141 voxels, peak T value: 2.14), bilateral precuneus (MNI: -2, -60, 30, 127 voxels, peak T value: 2.30), left angular gyrus (MNI: -48, -66, 40, 82 voxels, peak T value: 2.41) and right pre-SMA (MNI: 6, 0, 64, 51 voxels, peak T value: 2.18). Direct contrasts of the individual time periods against the mean of the other two revealed unique effects for all time periods. The Early period showed increased connectivity to candidate BPAS (bilateral precuneus, left paracentral lobule, middle temporal gyrus (MTG) and angular gyrus, right postcentral gyrus and supramarginal gyrus), DBAS (right IFG, p. Triangularis) and left putamen. The Middle period showed increased connectivity to candidate BPAS (left STG) and right caudate nucleus. The Late period showed increased connectivity to candidate DBAS (right SFG, left MCC) and caudate nucleus.

7.2.4: Suppression results

7.2.4.1: Suppression related activations

The [Suppress>Negative] contrast revealed increased activation in the Early and Late time periods, with stronger responses in the late period (see Appendix: Table 6; Figure 7). In the early period increased response was seen in motor control regions (right pre-SMA) and BAAS (anterior insula) areas. In the Late period areas showing enhanced response included regions previously reported as involved in conflict monitoring (bilateral anterior cingulate), self-awareness (bilateral superior frontal gyrus), automatic emotion regulation (left middle orbital gyrus, IFG, p. Orbitalis), visual processing (middle temporal gyrus), facial expression (right Rolandic operculum), attention shifting (superior medial frontal gyrus) and response inhibition (left IFG, p. Triangularis). To test our third hypothesis that no decreased activity of the BAAS will be evident during Suppression

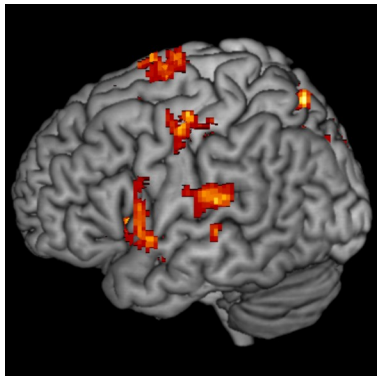
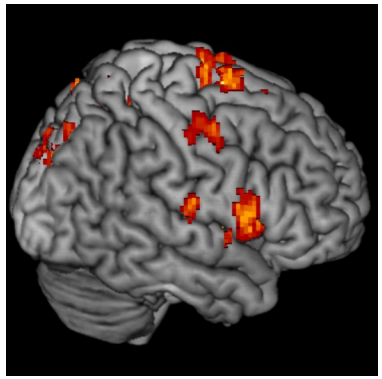
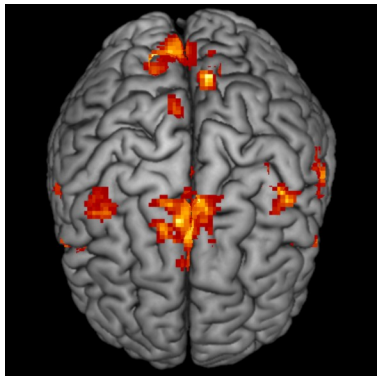
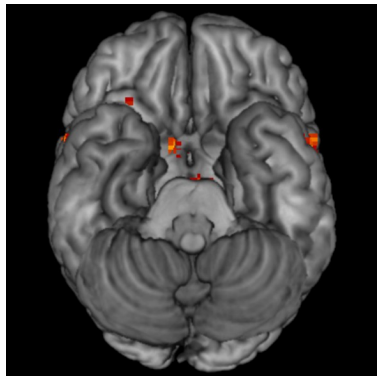
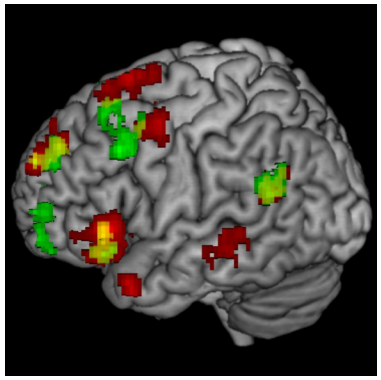
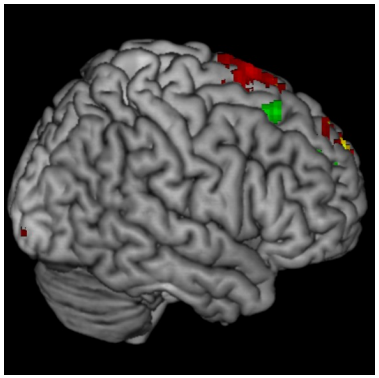
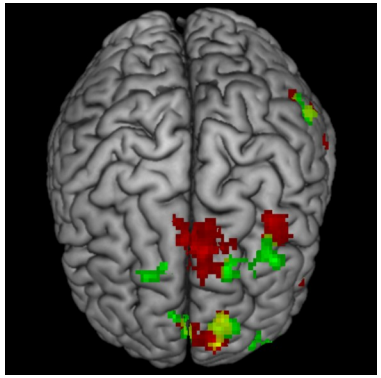
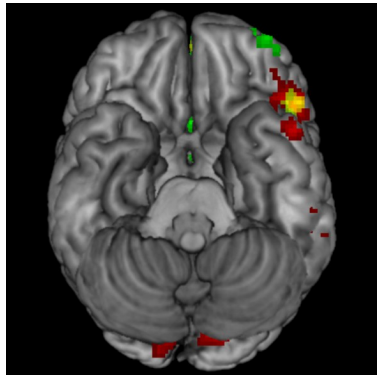
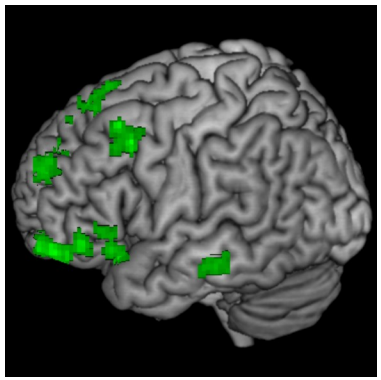
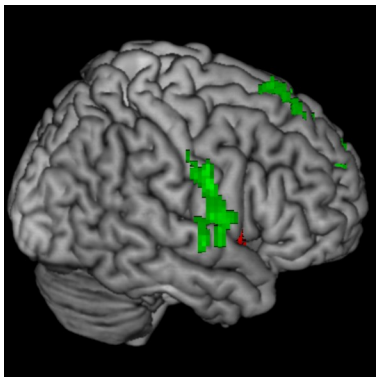
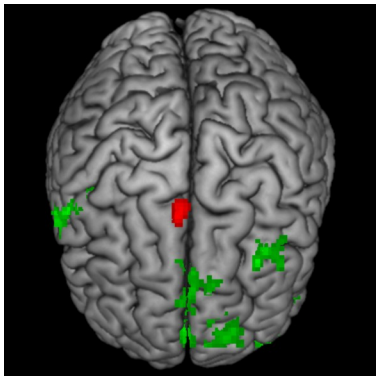
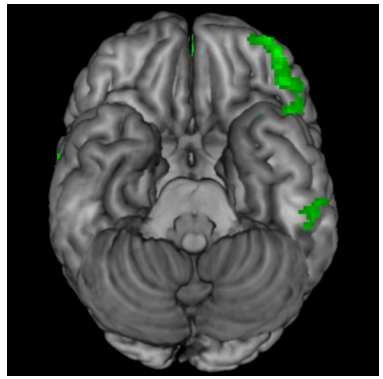
Contrast	*Left*	*Right*	*Top*	*Bottom*
Negative> Neutral				
Reappraise> Negative (Early & Late)				
Suppress> Negative (Early & Late)				

Figure 7: Increases of BOLD-signal for the [Watch-Negative>Watch-Neutral] blocks controlling for multiple comparisons at α<=.05 (p=<.001 & k=>31) and the components Reappraise Early(0-5) & Late(10-15), and Suppress Early and Late contrasted against the Watch-Negative Block. The component analyses were controlled for multiple comparisons at α<=.01 (p=<.005 & k=>50) For both strategies the increased signal for the early period is represented in red, and the late period in green. Yellow areas represent areas activated in both periods.

paired samples T-tests performed on PSC in the right and left insula in the Early, Middle and Late periods compared to the Watch- Negative condition. The results showed that there was no reduced emotion-related neural signal associated with Suppression.

To investigate overlap between time periods, direct comparison of the Early and Late periods contrasted against the negative-watch condition were performed by two-sample t-tests using SPM. Conjunction analysis revealed clusters in the right middle insula (MNI: 42, 8, 0, 75 voxels, peak T value: 3.64) and the left Rolandic operculum (MNI: -58, 8, 0, 55 voxels, peak T value: 2.25). Direct comparison of the early and late time periods using two-sample T-test (see Appendix: Table 7) revealed enchanced response in temporal and occipital visual areas (bilateral lingual and fusiform gyrii), attention areas (bilateral superior parietal lobule) and cognitive control (right SFG) and motor areas (left precentral gyrus) in the Early period. For the Late period relatively stronger responses was seen in large portions of the medial frontal lobe including bilateral ACC, right Rectal gyrus, and superior medial gyrus. In addition relatively stronger responses were observed in the right insula, bilateral medial and lateral orbitofrontal cortex and bilateral superior and medial temporal gyrus. Paired samples T-tests performed on PSC in the right and left insula in the Early, Middle and Late periods compared to the Watch- Negative condition showed no significant differences in neural activity in the insular areas identified in the emotion induction analysis.

7.2.4.2: Suppression related connectivity increases

The equivalent analyses as described for the RE condition were performed to test the fourth hypothesis that SE will result in BAAS being increasingly coupled with control and conflict monitoring areas as a function of time. The results (reported in Appendix: Table 8; Figure 8) showed that activity in the left insula was accompanied by task-dependent (Suppress>Watch-Negative) functional interaction with extensive cortical and subcortical regions. In the Early time period there was increased connectivity to areas involved in cognitive control (Superior Medial Gyrus), interoception (MCC) and motor control (pre-SMA). In the Middle period there was increases of functional interaction with areas involved in conflict monitoring (bilateral ACC), automatic emotion regulation (left middle and lateral orbital cortex), response inhibiton (right IFG), cognitive control (right superior and left middle frontal gyrii), motor control (bilateral precentral gyrus) and emotional expression (pallidum). In the Late period functional connectivity coupling was strengthened with areas involved in cognitive control (bilateral SFG and MFG), motor control (pre-SMA, precentral gyrus), emotional expression (right Rolandic operculum, right Putamen), automatic emotion regulation (left IFG, p. Orbitalis), somatic perception (left postcentral gyrus) and

associative visual perception (superior temporal gyrus). For the right insula seed (reported in Appendix: Table 9), increased functional connectivity was seen in the Early period to areas involved in automatic emotion regulation (bilateral middle orbital gyrus), action selection (bilateral MFG), motor control (pre-SMA), attention (left inferior parietal lobule, angular gyrus), categorical knowledge (left MTG), perception (posterior cingulate cortex) and thalamus.

Direct comparison the time periods was done by way of a one way repeated measures ANOVA using SPM. To investigate similarities between the time periods a conjunction analysis over all time periods was performed. For the left insula seed, conjunction analysis revealed clusters in the right MFG/SFG (MNI: 30, 46, 32, 325 voxels, peak T value: 2.76), left pre-SMA (MNI: -2, 20, 59, 124 voxels, peak T-value: 2.79), left supramarginal gyrus (MNI: 62, -34, 44, 117 voxels, peak T-value: 2.28) and right MCC/ACC (MNI: 8, 34, 37, 68 voxels, peak T- value: 2.29). Direct contrasts (see Appendix: Table 10) of the individual time periods and the mean of the two others to reveal unique contributions revealed an increase of connectivity to visual areas (right calcarine gyrus) for the Early period. For the Middle period increased connectivity to cognitive control (right SFG), facial expression (right Rolandic operculum), attention(right inferior parietal lobule) and visual areas (left calcarine gyrus) was shown. The Late period showed increased connectivity only to bilateral Rolandic operculum.

For the right insula seed, conjunction analysis revealed common increases in connectivity to left MTG (MNI: -48, -50, 10, 211 voxels, peak T value: 2.42), left STG (MNI: -52, -22, 2, 161 voxels, peak T value: 2.72), and right IFG (p. Orbitalis; MNI: 50, 24, -12, 89 voxels, peak T value: 2.77) , pre-SMA (MNI: 10,2,58, 80 voxels, peak T value: 2.07) and posterior MCC (MNI: 6, -18, 44, 64 voxels, peak T value: 2.20). Direct contrasts (see Appendix: Table 10) of the to identify unique effects were performed of the individual time periods against the mean of the two other periods. The Early period showed increased connectivity to areas involved in action selection (left MFG), interoception (right MCC), automatic emotion regulation (right middle orbital gyrus), emotion perception (left temporal pole) and visual perception (bilateral precuneus, bilateral parietal lobule) The Middle period showed increased connectivity to visual areas (left precuneus/calcarine gyrus) and right subgenual ACC, and area involved in emotional conflict monitoring and resolution. The Late period showed no unique increased connectivity.

7.2.5:Direct comparison of Reappraisal and Suppression

7.2.5.1: Direct comparison of activations

Direct comparison of RE and SE (contrasted with Watch-negative) was done by way of a 2 (ER: reappraisal, suppression) x 2 (time: early, late) repeated measures ANOVA in SPM. To investigate similarities between the two strategies in activation, a conjunction analysis of [(RE Early & RE Late & SE Early & SE Late)> Watch Negative] was performed. This revealed a significant 182 voxel cluster in the left IFG with maxima in the p. Triangularis (MNI: -52, 28, 0; T = 5.43) and the p. Orbitalis (MNI: -48, 30, -8; T= 4.04).

To investigate differences in activation between RE and SE, direct comparisons between them in each of the time periods (Early & Late) were performed using. The results from the Early (0-5 sec.) time period is reported in Appendix: Table 11. For the RE>SE contrast, enhanced response was seen in left lateralized areas of the frontal lobes including SFG, SMG, MFG, IFG and the midorbital gyrus. In addition enhanced response was seen in occipital areas including the left precuneus, middle occipital and angular gyrii, and the middle and superior occipital gyrus. For the SE>RE contrast, enhanced response was only seen in the right Rolandic operculum.

Results for the Late (10-15) period is reported in Appendix: Table 12. For the RE> SE contrast, enhanced response was seen in temporal regions, including bilateral hippocampus and middle and superior temporal gyrus, and the superior frontal gyrus. For the SE> RE contrast, enhanced response was seen in frontal regions (including bilateral middle cingulate cortex and paracentral lobule, as well as left IFG/MFG, Rolandic operculum, insula, and precentral gyrus), left temporal regions (including the temporal pole, hippocampus, parahippocampal gyrus, superior temporal gyrus and fusiform gyrus), parietal regions (including supramarginal gyrus, middle cingulate cortex, inferior and superior parietal lobule, postcentral gyrus and precuneus), occipital regions (including middle calcarine gyrus) and left subcortical regions (including putamen and thalamus).

7.2.5.2: Direct comparison of connectivity increases

Direct comparison of RE and SE (contrasted with Watch-negative) was done by way of a 2 (ER: reappraisal, suppression) x 3 (time: early, middle, late) repeated measures ANOVA in SPM. To investigate similarities in connectivity increases with the insula seed regions, a conjunction analysis of [(RE Early/Middle/Late & SE Early/Middle/Late)> Watch-Negative] was performed for each

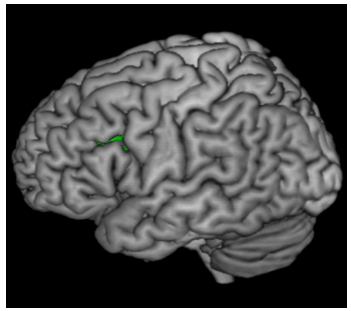
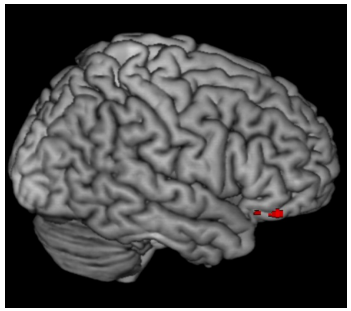
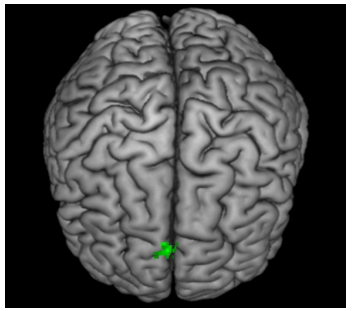
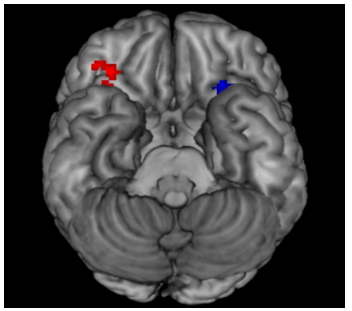
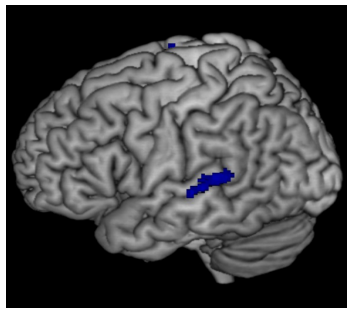
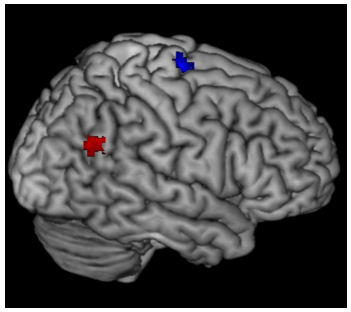
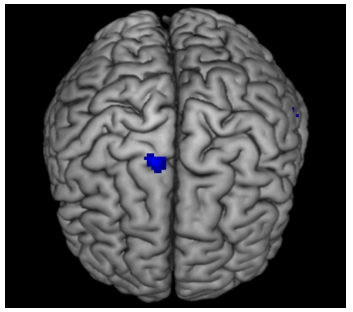
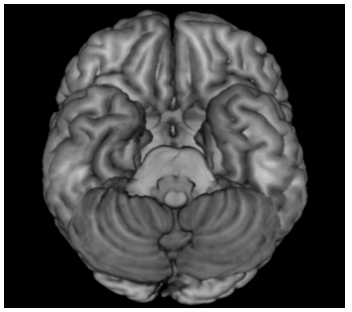
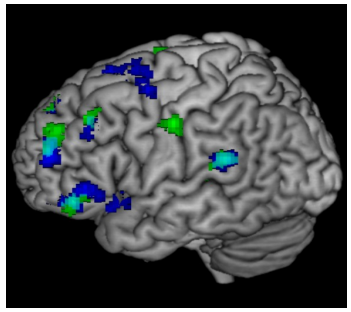
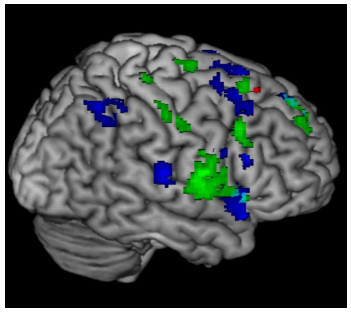
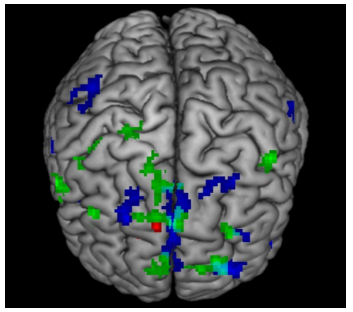
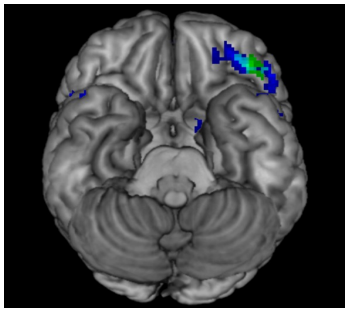
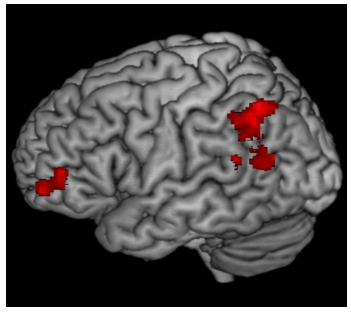
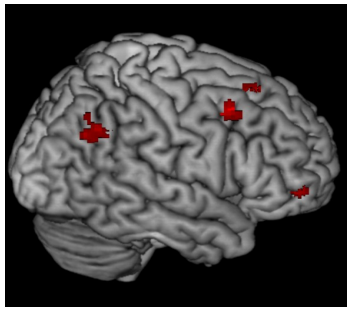
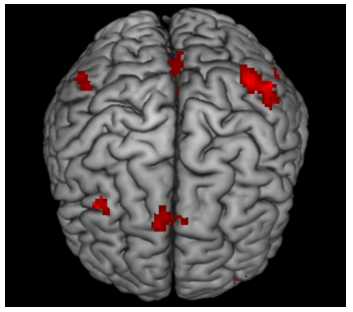
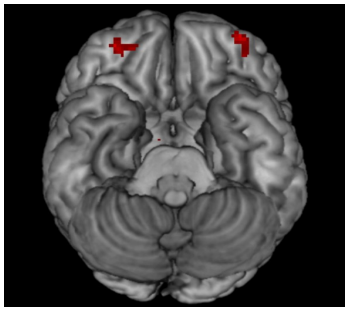
Seed/Condition	*Left*	*Right*	*Top*	*Bottom*
Left seed Reappraisal related connectivity change				
Right seed Reappraisal related connectivity change				
Left seed Suppression related connectivity change				
Right seed Suppression related connectivity change				

Figure 8. Increased functional coupling for Reappraise Early(0-5) & Late(10-15), and Suppress Early and Late compared with the Watch-Negative Block, controlled for multiple comparisons at α<=.01 (*p*=<.005 & *k*=>50). Red = Early period, Blue = Middle period, Green = Late period. Cyan areas represent overlap in functional coupling for Middle and Late periods.

seed region. This revealed no significant changes in connectivity common to both strategies in all time periods for either seed region.

8: Discussion

In this study, subjects regulated their emotional reactions to disgusting film stimuli, by using two different emotion regulation strategies that have been proposed to have different neural substrates and temporal dynamics. The hypothesis motivating this study was that these changes should be reflected in changes in activity of ER networks and BAAS areas as well as changes in connectivity between bottom-up emotional appraisal systems and top-down control systems as a function of both time and strategy.

8.1: Summary of results

The results both converge with and diverge from earlier findings and therefore both support and disagree with the guiding hypotheses about the anatomical substratum of reappraisal and suppression, the temporal dynamics of these strategies, and the changes in connectivity that underlie them. Emotion induction was predicted to result in widespread activity in BPAS and BAAS areas. The results supported this prediction, with evidence of extensive bilateral activations of the anterior insula, supporting the contention that this region serves as a bottom-up appraisal system for disgust related stimuli.

With regards to differing effects of the emotion regulation strategies on experienced negative affect, it was predicted that 1) RE would be superior to SE in reducing negative affect, but that 2) SE also would result in reduced negative affect relative to the unregulated condition. The behavioural results established the successful use of reappraisal by subjects, with significant reductions in negative affect. The results also showed that the suppression strategy also was effective at reducing negative emotion. However, as predicted, direct comparison of the two strategies showed the relative superiority of the Reappraisal strategy for the reduction of experienced negative affect.

Several specific hypotheses about the individual ER strategies were made. RE was predicted to elicit activity in superior frontal areas subserving the DBAS and inferior frontal areas, subserving the OBAS, as well as temporal, parietal and occipital areas subserving the BPAS. The results conform with our primary hypothesis for RE, in that evidence of activity was seen in a number of the candidate regions for the DBAS, OBAS and BPAS. With regards to the time course of RE, it

was predicted that evidence of activity in these areas would be evident only in the early period of the emotional event. The results partly conform with this prediction, since evidence was seen in the predicted areas in the Early period. However, in contradiction to earlier work and our prediction, activity in mainly the same regions was also seen in the Late period. Of note is the considerable overlap between activity in the Early and Late periods, indicating reactivation of the same network in the Late period. Conjunction analysis showed that the p. Triangularis and p. Orbitalis portions of the IFG were activated during both time periods. RE was also predicted to result in decreased activity in the BAAS in later periods. Again, the results partly conform with this prediction, in that a significant drop was seen in the Late period. Unexpectedly this was also the case in the Early period. The results indicates that reductions of activity in the insula were equivalent for both Early and Late periods, with a rebound of activity in the Middle period. Finally, it was predicted that connectivity between the BAAS and OBAS would be increased in the Early period, while connectivity to BPAS would increase in later periods. Again, the results partly conform with our hypotheses. The left insula showed increased connectivity to differing OBAS candidate areas during the entire time course, while the right insula shows increased connectivity to BPAS during Early and Middle periods only.

In contrast to RE, SE was predicted to elicit activity in frontal areas involved in motor control, executive control and response inhibition, as well as areas involved in conflict-monitoring. The results conform with this prediction, in that enhanced response is seen in a number of regions involved in conflict monitoring, response inhibition and executive motor control. With regards to the time-course of SE activity, it was predicted this activity will be largely apparent in late periods of the emotional event. The results partly conform this hypothesis since activity in motor control areas (i.e. the pre-SMA) was only seen in the Early period. SE was also predicted not to have any differential effects of BAAS activity. This prediction was confirmed by the results. Finally, it was predicted that SE would show evidence of increased coupling of the BAAS and control and conflict monitoring areas as a function of time. The results support this hypotheses in that the left insula seed show the predicted increases in coupling as a function of time.

8.2: Comparison with earlier findings

8.2.1: Activation results

The central prediction regarding the unregulated emotional results were that they would show evidence of activity in the candidate BAAS areas amygdala and insula and striatum and OFC.

This was partially supported, with increased activity observed in bilateral insula, and the caudate nucleus of the striatum. The amygdala, however, did not show evidence of increased activation, nor was there evidence of increased activity in OFC. There is however a fair degree of overlap between the results of this study and those presented in previous work. The anatomical areas involved are mostly the same, being centered on visual, attentive and candidate bottom- up emotional appraisal systems (i.e. the agranular anterior insula). The absence of amygdala activation is somewhat discrepant from earlier findings. One possible reason for this is that the earlier study by Goldin et al. (2008) seem to have confounded several dimensions of the film stimuli. First, the stimuli used were potentially fear-inducing due to the startling nature of most of their film clips. While the current study employed stimuli that were specifically selected to avoid indications of threat by focusing on the visceral and component of disgust (i.e. vomit, blood) in otherwise neutral, but obvious, contexts (e.g. surgical procedures), the previous study included both films of animals being slaughtered in a violent fashion and contextless films of limbs being severed. Second, the neutral stimuli used to establish the regions representative of the BAAS were not matched to the emotion inducing stimuli on the basis of visual properties. The neutral stimuli in the earlier study were films of tranquil nature scences, whereas the current study used films selected to include as many as possible of the stimulus properties of the emotion inducing stimuli. Given the involvement of the amygdala in novelty detection (Barrett, Bliss-Moreau, S. L. Duncan, Rauch, & Wright, 2007), this might indicate that the amygdala activations seen in other studies might be a consequence of the relative novelty and "otherness" of the emotion inducing stimuli versus the neutral stimuli than the actual involvement of the amygdala in the evocation of experienced disgust. This might also explain the more widespread activation reported in the earlier study, relative to the more concentrated network found in the present study.

The greatest, and perhaps most important, discrepancies between the current and previous findings is within the domain of the temporal dynamics of reappraisal. The results coincide with those of Goldin et al (2008) and the previously discussed ERP- results in showing that there is a distinct pattern of activation of brain areas involved in emotion regulation immediately following stimulus onset. However, the current analysis also indicates that there is a hitherto undescribed, and unpredicted late activation pattern associated with reappraisal, consisting of many of the same areas as those seen in the Early period. In addition the current study found evidence of SE related activations in the early stages of the emotional event, which the Goldin et al study did not. There are several possible explanations broadly attributable to i) data and preprocessing parameters and ii) the analysis methods employed.

With regards to data aquisition and preprocessing there are two main issues. First, the data aquisition parameters employed by the respective studies differ in several respects. The first potential issue is the spatial resolution of the data. The previous study employed a voxel size of ca. 61 cubic mm per voxel, whereas the current study acquired data on the significantly finer resolution of 11 cubic mm per voxel. In addition the previous study smoothed the data with a kernel effectively smaller than each voxel (4mm^3), thus rendering the data relatively more sensitive to peak values of voxels. The current study, however used a kernel larger than the voxel size , thus sensitizing it to clusters of voxels moreso than peak values. While there are advantages and disadvantages to both of these approaches, it is reasonable to assume that the current study reflects better the contribution of larger assemblies of neurons than the earlier study. Given the tendency of neural networks to go from specificity to generality in the unfolding of a given task, it is reasonable to assume that the current analysis is more sensitive to the later parts of the emotion regulation process than the earlier study. Second, the preprocessing steps employed differ markedly in that the current study employed a pipeline explicitly geared towards retaining the anatomical specificity of the data by incurring as little unwanted smoothing by interpolation as possible. The current study also employed the DARTEL method of normalisation which has proved superior to other commonly employed methods in retaining the anatomical localization of functional data after normalisation (Klein et al., 2009).

With regards to differences in analysis methods there is one issue with regards to analysis methods employed at the subject level, and two with regards to the group level statistical methods and inference of significance. First, the previous study employed a traditional convolvement of a hemodynamic gamma variate function with a boxcar reference function. This method is, as has been discussed previously, potentially vulnerable to variability in BOLD response as a function of the evolving dynamics of an event. In addition, there is the risk of incurring a loss of sensitivity due to correlations between the reference functions, that would result in variance properly attributed to later regressors being attributed to the first. The current study avoids this problem by using a stick reference function convolved with a gamma variate function that is allowed vary in onset, peak, as well as dispersion. This results in increased sensitivity for BOLD- inducing activity that does not follow a strict ON-OFF pattern, as a boxcar function would predict.

Second, the current study explicitly includes a measure of reappraisal success in the modelling of ER activity. The implementation of this was achieved using robust regression, a method that has proved successful in controlling for the biasing effects of outliers that might drive

spurious effects, or conceal actual ones. No similar correction was employed in the previous study.

Finally, the previous study employed an exceptionally strict alpha value of .001 for the block analyses and .005 for the component analysis, as opposed to the more common levels of .05 and .01. Hence the previous study was biased in favor of protection against Type I errors. This however comes with the penalty of increasing the amount of Type II errors made. This is evidenced by the fact that using the same alpha value in the current analysis yields results that are essentially identical to those reported by the previous study.

In summary, the present study differs from the previous study in that it is more sensitive for anatomically specific functional clusters and their temporal dynamics with a lower suceptibility for type II errors, while providing adequate protection against type I errors. These points, combined with the larger sample size, and the inclusion of both genders in the sample warrants the tentative conlusion that the current study better reflects the general network for cognitive emotion regulation through reappraisal and its temporal dynamics than the previous study.

8.2.2: Connectivity results

The current study on the functional connectivity changes related to cognitive reappraisal both confirms and extends the findings by Banks et al (2008). Reappraisal was consistently shown to alter the connectivity properties of the anterior agranual insula with areas shown in the current and earlier study to be involved in emotion regulation. There are, however, some differences, including the bilateral activation of bottom-up affective appraisal systems, as well as differences in the precise areas showing changes in connectivity. These differences may stem from i) the emotional response induced, ii) the stimulus modality employed, and iii) the time period of the emotion regulation process focused on in each study.

First, the Banks et al (2008) study employed stimuli that were selected on the basis of the two factor model of emotional stimulus properties (i.e. arousal and valence), whereas the current study employed stimuli that were specifically disgust-inducing. This might account for the differences in connectivity between the current and the previous study. Conversely, it is possible that the regions showing connectivity changes in both the current and the earlier study might represent a general emotion regulation network that's independent of the specific negative emotion regulated. Second, the earlier study used a blocked presentation of static picture stimuli (5 x 4 second presentations per block) whereas the current study employed film stimuli that were analysed

on a trial by trial basis. Given these considerations, it is reasonable to assume that the Banks et al study reflected a mean of the entire emotion regulation process. This hypothesis is supported by the current results, in that, if taken as a whole, the current study shows changes in connectivity that to a large degree overlaps with those reported by the earlier study.

In summary, the current results on functional connectivity of the insula attributable to reappraisal are primarily consistent with earlier findings. Differences in results might reflect the specificity of the stimulus material employed in this study, and differences in experimental design. The overlapping results, however, might reflect a core emotion regulation network employed regardless of induced emotion.

8.3: Temporal dynamics of activation and connectivity in Reappraisal

To a large extent the current findings show similar activation patterns as earlier studies of ER using fMRI. Conjunction analysis revealed the core areas involved in RE process to be frontal candidate DBAS areas, such as the left IFG, medial PFC and pre-SMA, in addition to temporal lobe areas involved in language processing (Noppeney & C. J. Price, 2002; C. J. Price, 2000). Connectivity analyses nuance these results by showing that RE is related to increased connectivity between the left BAAS and OBAS and DBAS, preferentially in left hemisphere. For the right hemisphere BAAS there is in evidence of increased connectivity to BPAS areas. The activity seen in the Early period of the RE condition, is likely to reflect the initial formulation and implementation of the RE strategy. The results indicate that this relies heavily on the recruitment of BPAS areas, as well as areas involved in the regulation of physiological emotional responses (middle cingulate cortex; Diorio, Viau, & Meaney, 1993; Gamer, Bauermann, Stoeter, & Vossel, 2007) and language processing (left IFG, p. Opercularis; eg. Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004). Connectivity results support and differentiate the activation results, in that the implementation of the RE strategy results in increased coupling between the BAAS and OBAS and BPAS areas in the earlier stage of the RE condition, with the right BAAS again showing increased connectivity to BPAS areas of the and the left BAAS to OBAS areas. Activity unique to the Late period is likely to reflect the maintenance of the strategy over time. The activation results indicate that this relies on DBAS areas involved in attentional control (right SFG; Hampshire, Thompson, J. Duncan, & Owen, 2009) and self- related processing of agency (right SMG; Cooper et al., 1995) and response inhibition (right putamen; Kelly et al., 2004). Connectivity results are congruent with the activation results, showing increased connectivity between BAAS and DBAS involved in response inhibition and attentional control, as well as OBAS areas involved in self-

related processing as being the unique component of RE connectivity in the Late period.

These findings might reflect that the proposed regulatory effects afforded by DBAS through modulation of BPAS are preferentially subserved by right lateralized networks, while the verbal, rule based part is subserved by left lateralized networks. This would be in accordance with a recent meta-analysis (Costafreda, Brammer, David, & Fu, 2008) which found that verbal stimuli more reliably elicited increased activity in the left amygdala (a central part of the BAAS, as previously discussed). In contrast activity of the left amygdala was reliably elicited by masked visual stimuli. The authors interpreted this as being a possible neural substrate for the findings of Olsson and Phelps (2004). In their experiment an association was made between a conditioned stimulus (angry face) and either a real shock, the verbal threat of a shock, or the observation of a shock given to someone else. When the angry face was overtly presented, all three groups showed evidence of conditioning as measured by increased skin conductance relative to an unconditioned angry face. When the stimulus was masked, only the group with the language dependent link failed to show the same evidence of conditioning. The authors concluded that the lack of response may be due to a relative failure of right lateralized information about the masked stimulus reaching left lateralized language knowledge of its learned value.

A special characteristic of the emotion disgust is that it (with the exception of gustatory disgust and so called core disgust related to bodily threats; Rozin et al., 2008) shows a developmental trajectory, typically emerging at age 3-5, and requires culturation to take form (reviewed in Rozin et al., 2008). Thus, most disgusting stimuli are in fact not innately disgusting, but rather have acquired this property by individual learning the culturally appropriate appraisals for disgusting stimuli. This is to say that most disgusting stimuli acquire their affective meaning through language-based learning. Evidence was discussed in the introduction indicating that RE operates in a similar fashion as extinction learning (Phelps, 2006). Extinction learning occurs when a conditioned stimulus (CS) is presented alone, without the unconditioned stimulus (US), for a number of trials or an extended time period and eventually the conditioned response (CR) is diminished or eliminated. If this is the case, then the current results might reflect RE interrupting the link between the CS (the disgusting properties of the film) and the CR (negative affect). It is possible that DBAS modulates BPAS, providing alternate reinterpretations that effectively "mask" the immediate appraisal of the emotional stimuli, with alternate perceptual interpretations in the right BAAS. This happens in conjunction with the verbal reinterpretation of the disgusting properties of the stimulus having its effects on directly updating the reinforcement contingencies

(i.e. the context) of the stimulus by way of the left hemisphere OBAS, which again influence the left hemisphere BAAS.

If this is the case this might also explain the fact that in this study evidence was seen of a rebound in BAAS activity in the Middle period of the RE condition. This might reflect a similar effect as that reported by Walter et al. (2009). This fMRI study explicitly studied the aftereffects of reappraisal in the period following offset of regulated stimuli and found a rebound in amygdala activity following reappraisal. The amplitude of this rebound was negatively correlated with sustained emotion regulation effects. This effect might be akin to results in the literature on extinction learning showing spontaneous relapses of CR after extinction learning in a number of different circumstances (see Bouton, 2002 for a review). If this is also the case in the current study, this might explain the resurgence of activity of the RE network in the Late period. A possible sequence of events might be for the Early period 1) stimulus presentation, 2) RE network engagement, 3) successful reduction of BAAS activation (and, presumably, negative affect). In the Middle period this will result in 4) deactivation of RE network since there is no longer negative affect to be regulated, and therefore 5) a rebound of BAAS activation leading to 6) increased negative affect. Thus, in the Late period we see 7) reengagement of the RE network and 8) successful decrease of negative affect (as reflected in post- film ratings) and BAAS activity. While the neural components investigated in this study track this sequence of events, it is impossible to verify if this model is correct, since we have no independent measure of emotional activation tracking the time-course of the emotional event. Including measures of e.g. SCR and/or pupillometry in future studies in future studies would help in investigating this sequence of events. Another open question is whether these dynamics are time-locked to the stimulus presentation, or reflect the general dynamics of the RE strategy. An investigation of this would provide insight into the exact nature of the spontaneous relapse, and thus provide further insight into the relationship between extinction learning and reappraisal. Including stimuli with varying duration in future studies, might provide an answer to this question.

8.3.1: Updating the working model of Reappraisal

Our working model proposed that RE was subserved by two distinct systems, the DBAS and the OBAS. The current results supports this model, and expands on it by adding a layer of temporal dynamics. In accordance with RE being an antecedent- focused emotion regulation strategy, these effects are apparent both in neural activity and connectivity changes to the BAAS areas after a short time period. RE results in immediately increased activity in DBAS, OBAS and PBAS areas,

reflecting the implementation of the ER strategy by neural systems. This affords a reduction of activation in the BAAS, associated with increased coupling between the left lateralized BAAS and OBAS, and right lateralized BAAS and BPAS. The patterns of activity and connectivity observed indicate a mechanism of regulation that can be interpreted as being similar to what has been seen in extinction learning, supporting the contention that conscious emotion regulation through reappraisal is supported by the same mechanisms that effect unconscious regulation of emotion.

8.4: Temporal dynamics of activation and connectivity in Suppression

The current study found SE related activity in the early stages of the emotional event, notably in the pre-SMA. Since this region has been implicated in the representation of intentional action (M. Brass & Haggard, 2008) and orienting to and responding to internal clues (Stuss & M Alexander, 2007). The pre-SMA has been shown to be consistently activated in a wide range of neuroimaging studies of emotion. Based on this Kober et al. (2008) has proposed that it is a part of a cognitive/motor network involved in shaping the behavioural and physiological responses to an emotion via reciprocal projections to BAAS areas. As such, the activity observed in the pre-SMA might reflect the implementation of the expression suppression strategy. The interpretation that the current results reflect this is supported by the direct contrast of the Early against the Late period, which showed increased activity in primary motor cortex, that might reflect engagement of these areas in effecting motor inhibition of the facial muscles.

In the conjunction analysis over time periods, reflecting activity common to both the Early and Late periods, the Rolandic operculum (RO) was shown to be activated. This was also the case in analyses of the unique activation related to SE in both time periods. This area has in previous studies mainly been implicated in emotional processing and generation of emotional prosody (Kotz, Meyer, Alter, von Cramon, & Friederici, 2003) and emotional responses to auditory stimuli (Koelsch et al., 2006). However, a case study by Sim et al. (2005) reported a patient that presented with a selective loss of volitional emotional facial movements after a bilateral acute infraction in the RO. Irregularities in this region has also been implicated in Foix- Chavany- Marie (FCM) syndrome, which is characterized by, amongst other things, facial paralysis (Bakar, Kirshner, & Niaz, 1998). Interestingly, automatic motor control, such as that involved in emotional expression, of craniofacial muscles is preserved in patients suffering from FCM, indicating that the RO plays a specific role in voluntary control of facial muscles. Accordingly, it might be that the activations of the pre-SMA and RO reflect the neural substrates of Suppression-related inhibition of facial expression.

The patterns of connectivity increases to the insula seed regions are largely supportive of this possibility. In the Early portion connectivity from both seeds increased to pre-SMA as well as cognitive control areas, possibly reflecting the initial setting up of a cognitive motor control network akin to the working model that was proposed for SE. This hypothesis is strengthened by the connectivity increases seen in the Middle and Late periods for the left insula seed, since the coupling with SFG remains significant for the entire emotional event. This area has been implicated in the higher levels of working memory processing, including monitoring and effecting manipulations (Boisgueheneuc et al., 2006). This points to this region being involved in the continued monitoring of the bottom-up emotional response, which corresponds to the what one would expect of the comparator component of the model. The pre-SMA did not show increased activation, nor increased connectivity to the insula in the Middle period. This can be explained if the pre-SMA in deed is the implementor of the facial inhibition involved in SE, since control is not needed unless a discrepancy is detected, or predicted, by the comparator. The results indicate a substantial increase of both activity in and connectivity to areas involved in response inhibition, cognitive control and conflict-monitoring areas in respectively the Late, and Middle and Late periods. This is possibly indicative of increasing conflict between the SE strategy and bottom-up emotional expressive behaviour. In support of this hypothesis, connectivity between the left insula and areas involved in emotion expression (i.e. striatum; Iwase et al., 2002; Trosch, Sze, L. M. Brass, & Waxman, 1990) is also seen during the Middle and Late periods. This might reflect increasing bottom-up demand to elicit the emotional response, thus increasing the conflict between top-down and bottom-up influences.

8.4.1: Updating the working model for Suppression

Our working model proposed that SE could be thought of as the coupling of a general behavioural self-regulation network coupled to the modal model of emotion. This contention has to a considerable degree been supported by the present research. In the early stages of an emotional event, a motor inhibitory network seems to be set up based on the pre-SMA as the control system, the SFG as the comparator and the Rolandic operculum as the substrate being controlled. However, it has also been shown that SE likely involves a second system, namely a conflict monitoring and resolution network brought online by the discrepancy between the bottom-up emotional response tendencies and the top-down expression inhibition. Thus, the temporal dynamics of activity and connectivity involved in suppression point towards it involving two distinct, but interconnected systems. In summary, the current study indicates that the behavioural self-regulation network comes online in the early epoch of an emotional event, inducing a conflict with the BAAS response, that

requires the recruitment of a conflict resolution system in the later stages of the the event.

8.5: Is there a core volitional emotion regulation system?

Hitherto we have discussed the two ER strategies that are the subject of the current study as independent, and therefore being implemented by distinct functional systems, and, by implication, by distinct neural networks. The current study investigated both unique and common patterns of activity and connectivity related to both RE and SE. Conjunction analyses revealed significantly increased activity in the left IFG. This might indicate that the supposition that SE and RE are functionally uncoupled is false, despite the differences in how these strategies are implemented and their regulatory focus.

There is a growing body of evidence indicating that certain areas of the prefrontal and cingulate cortices are activated irrespective of which specific emotion regulation strategy is employed. McRae et al. (2010) investigated the neural bases of cognitive reappraisal (i.e. RE) and the ER strategy of attentional distraction using fMRI and picture stimuli. According to the process model of emotion regulation discussed earlier, attentional distraction is another species of antecedent- focused ER, focusing on preventing emotional activity through not attending the emotional stimulus (see also the earlier discussed modal model of emotion). As such it is predicted to differ substantially from RE both in efficacy and with regards to the specific systems involved. The results showed that, while RE and attentional distraction had significantly different activation patterns, there was also a considerable degree of overlap between the two. This overlap included areas (amongst others) the IFG. Another ER strategy that has been investigated to some extent is detachment. This strategy focuses on reducing the relevance of emotional stimuli by taking the stance of a neutral observer. Detachment is similar to RE in that it involves an active cognitive manipulation of the emotional stimuli. It differs, however, in that it does not attempt to reformulate the emotional significance of the stimuli, but rather the relevance of the stimuli to oneself, and should therefore have differing activation patterns centred on areas involved in self-referential cognition, primarily the dorsomedial PFC (dMPFC). Four fMRI studies (Eippert et al., 2007b; Kalisch et al., 2005; Ochsner et al., 2004; Walter et al., 2009) have hitherto investigated detachment, all except one (Kalisch et al., 2005; pain stimuli) using picture stimuli. All four studies have reported the predicted increased activation of the dMFPC. In addition to this, however, all except one study (Eippert et al., 2007) also found increased activity in areas roughly corresponding to the pars Triangularis and pars Orbitalis subsections of the IFG. Finally, one earlier study (Goldin et al., 2008) has directly contrasted RE and SE, the same strategies that are the subject for the

current study. Falling in line with the studies discussed above, this study reported activations of the IFG following implementation of both RE and SE, albeit with different laterality (RE: left, SE: Right) and in different periods of the ER events (RE: 0-4,5 sec, SE: 10,5-15).

It therefore seems that the IFG is a candidate area for a core ER system. This region has been implicated in, amongst other things, prosodic language processing (Friederici, 2009), cognitive control of memory (Bunge, 2004), multimodal response inhibition (Chikazoe, Konishi, Asari, Jimura, & Miyashita, 2007; Swick, Ashley, & Turken, 2008), emotional prosody (Buchanan et al., 2000), emotion perception (Barrett, Kristen A Lindquist, & Gendron, 2007), empathy (Lamm, Meltzoff, & Decety, 2010), emotion-related attentional control (Pessoa, Rossi, Japee, Desimone, & Ungerleider, 2009) and executive control and conflict resolution in working memory (Feredoes, Tononi, & Postle, 2006; Postle et al., 2006). This region therefore seems suited to effect emotion-related cognitive control in a variety of situations, including both SE and RE strategies.

This hypothesis is supported by evidence (Johnstone, van Reekum, Urry, Kalin, & R. J. Davidson, 2007) that depressed individuals, relative to non-depressed individuals, show a disruption of the relationship frequently reported between the left IFG and the OBAS (e.g. Urry et al., 2006), during emotion regulation tasks. Instead they show an strengthened relationship between OBAS and amygdala, possibly reflecting a disconnect between the volitional and automatic components of the emotion regulation network. In contrast to this individuals suffering from apprehension anxiety (i.e. anxiety related to cognitive worry, in contrast to arousal based anxiety, such as panic attacks) have been reported to have increased activity in the left IFG in response to negative words (Heller et al., 2008). It is possible that this increased activity is reflecting of the cognitive up-regulation of negative emotion in response to environmental threats. Support for this top-down role of the IFG is found in a recent fMRI study tasked subjects with deciding the valence (positive or negative) of emotional prosody in spoken sentences with congruent or incongruent semantic contents (Wittfoth et al., 2009). The left IFG was found to be preferentially activated in the congruent relative to incongruent conditions. The authors interpreted this as the IFG being involved in the decoding of emotional prosody in a conflicting semantic context, without specifying how it is involved. One possibility, based on the findings reviewed above, is that the IFG resolves the conflict through influencing OBAS, providing a top-down context for the interpretation of the stimulus. The OBAS in turn may then influence BAAS areas, focusing them on the prosodic aspect of the stimulus, resulting in a resolution of the conflict.

Support for this model of IFG influence is found in a recent fMRI study using mediation analysis to establish the effective connectivity of the right vlPFC (i.e. IFG) during reappraisal (Wager, M. Davidson, Hughes, M. Lindquist, & Ochsner, 2008). As mentioned earlier, effective connectivity refers to the influence a brain area has on another. Thus this study provides an insight into the causal dynamics of the IFG during one emotion regulation task. In support of the previously proposed model of IFG influence, the results indicated that the IFG modulated BAAS areas, and that this modulation was mediated by central OBAS areas, specifically the medial OFC and VMPFC. Summarizing these findings it is evident that the IFG is an essential component of at least one emotion-regulation task, and frequently reported as a component in a series of other tasks including those investigated in the current study. This region has also been implicated in the pathophysiology of a subtype of anxiety and in depression. Despite this it is still an open question exactly what function the IFG performs in these emotion-regulation tasks.

Returning to to our working model of Suppression there is still one essential component hitherto unaccounted for by the present results. Initially we hypothesized, based on the findings of the earlier Goldin et al. study, that this function was performed by the dorsolateral PFC. We also assumed that the ventrolateral PFC (i.e. IFG) was responsible for inhibitory motor control. However, the present connectivity evidence seems to indicate that the dorsolateral PFC (i.e. SFG) is performing the comparator function. The inhibitory motor control control component seems to be better accounted for by the dynamics of neural activity in and connectivity to the pre-SMA, rather than the IFG (i.e. ventrolateral PFC). Thus we have yet to account for the component responsible for setting the reference state. This is also the case for Reappraisal. While not an explicit component of the DBAS/OBAS model proposed by Ochsner and Gross (2007), the reference state it is nonetheless an essential component for initiating RE, and in fact, any cybernetically modelled goal-driven regulatory process (Carver & Scheier, 1998; Magen & Gross, 2010). Thus, if there is evidence of activity common to both strategies, it is likely that it identifies the one common component of them both- i.e. the system responsible for setting the reference state. It therefore seems reasonable to propose that the pars Triangularis and pars Orbitalis portions of the left IFG together might constitute a central and common component of many, if not all, tasks involving emotion-related regulation. The current results indicate that, while the IFG is consistently activated across time periods in both strategies, there are no consistent changes in connectivity between the two strategies. While the interpretation of a null-finding is difficult, this might point towards the IFG recruiting task- relevant areas of the brain as a function of the goal of the regulatory process. In other words, the IFG might perform an essential function in volitional emotion regulation by

setting the reference state (based on the conscious goal) for task-specific control networks that affords direct influence on the goal-relevant systems, be they motor-control related (as in the case of suppression), or emotion-experience related (as in the case of reappraisal).

8.6: Limitations

There are two central methodological limitations in the current study, and two limitations with regards to generalizability of the results. The central limitation of the present study is the lack of an independent measures of emotional state (such as SCR, or facial expression recordings). A second limitation is the lack of an independent check on efficacy of suppression except for subject´s subjective report post scanning. Addresing these limitations by adding such measures in future research would allow one to independently check all components of the emotional response, to ensure ER efficacy and further examine the temporal dimension of ER. A third limitation is with regards to generalizability of the models presented, since they are based on the regulation of disgust exclusively. It is not known whether these findings will generalize to other emotions. Finally, it is not known if these findings will generalize across cultures. All participants were of Norwegian heritage, and there is some indication that the consequences of emotion regulation through suppression is conditioned by the cultural context (Butler, Lee, & Gross, 2007). To facilitate cross-cultural investigations of emotion regulation, it would be advisable to continue the development of a standardized set of emotion-inducing films that can be used in relation neuroimaging.

8.7: Conclusion

The present study provides evidence that the emotion regulation strategies Reappraisal and Suppression are subserved by both common and distinct neural networks. These networks differ in their temporal dynamics both with regards to activity in brain areas, and connectivity between brain areas. The current results concur with previous studies in indicating that Reappraisal is subserved by two distinct top-down appraisal systems, that affect the both emotion- related perceptual and affective bottom-up appraisal systems. The temporal dynamics of activations and connectivity changes related to Reappraisal were interpreted as indicating that Reappraisal might be best understood as a consciously initiated controlled extinction learning process. Suppression in turn was found to be subserved by two distinct networks, one motor control network and one conflict monitoring network hypothezised to be involved in mediating the conflict between the inhibitory motor control and prepotent emotional response patterns. The temporal dynamics and connectivity patterns were interpreted as supportive of this hypothesis. Furthermore, evidence was found that both of these strategies are characterized by activity in a region of the brain implicated in emotion-

related control in a wide variety of studies. This is interpreted as evidence for the existence of a core emotion regulation network centred on the IFG, that affords emotion- related regulation through the setting of reference states for other, task-specific, control networks.

Because the study only indirectly supports this hypothesis, future research will need to directly investigate the role of the IFG in recruiting other brain areas, preferably with methods that afford conclusions about the effective connectivity dynamics of this area. Future research should continue in the vein of the current study in investigating both the similarities and differences between different emotion regulation strategies. One possible benefit from this is a more nuanced insight into the neuronal architecture and dynamics of emotion-regulation, and ultimately into the pathophysiology of psychiatric disorders characterized by dysregulation of emotion. Another, more theoretical, benefit is that by investigating the commonalities and differences in the systems underlying different modes of emotion regulation it is possible to contribute to "neurologizing the psychology of affect" as Panksepp (2007) advocates. Doing this might contribute in shedding light on the nature of emotion itself, and thereby contribute to the furthering our understanding of one of the perennial subjects of human intellectual endeavour.

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10: Appendix

Table 1. Whole brain results for the contrast [Watch-Negative>Watch-Neutral] corrected for multiple comparisons at α= .05 (p<.001 & k>31). Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus

Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
	Frontal lobes			
L	Presupplementary Motor Area/ Midddle Cingulate Gyrus	-4, -10, 72	1406	6.49
R	Anterior Insula/ IFG (p. Opercularis)	38, 18, 6	455	6.12
R	Middle Frontal Gyrus/Postcentral Gyrus	42, -4, 52	171	4.91
L	Anterior Insula	-40, 16, 6	146	5.77
L	Precentral Gyrus	-46, -14, 61	86	5.94
R	Rolandic Operculum	58, -14, 19	50	5.24
L	Ventral Insula	-38, -6, -9	41	5.23
	Temporal lobes			
L	Temporal pole/ IFG (p. Opercularis)	-60, 6, 0	177	5.36
L	Middle Temporal Gyrus	-56, -28, 3	37	5.08
L	Inferior Parietal Cortex/ Superior Temporal Gyrus	-58, -28, 19	139	5.95
	Parietal lobes			
R	Precuneus	8, -56, 63	49	4.70
R	Superior Parietal Lobule	8, -46, 52	282	5.97
L	Precuneus/ Superior Parietal Lobule	-8, -72, 58	67	6.82
L	Postcentral Gyrus	-36, -26, 52	51	5.47
L	Superior Parietal Lobe	-16, -44, 46	38	4.94
	Occipital lobes			
R	Cuneus/ Calcarine Gyrus/ Superior Occipital Gyrus	22, -68, 22	2689	7.49
	Subcortical regions			
R	Caudate nucleus	8, 2, 5	47	5.85
Bilateral	Thalamus	4, -20, 2	316	6.79

Table 2. Whole brain results for the [Reappraise> Watch] component contrasts corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$). Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus

Component	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
RE Early		***Frontal lobes***			
	L	Presupplementary Motor Area	-4, 13, 60	578	5.56
	L	IFG, p. Triangularis/IFG, p. Orbitalis	-46, 30, -11	424	6.95
	L	Superior Medial Gyrus/ Superior. Frontal Gyrus	-14, 58, 35	261	5.57
	L	Precentral Gyrus	-40, -4, 60	140	5.08
		Parietal lobes			
	L	Inferior Parietal Cortex	-48, -60, 27	114	3.96
		Temporal lobes			
	L	Medial Temporal Pole	-52, 16, -25	57	5.30
	L	Middle Temporal Gyrus	-54, -32, 0	254	4.40
		Occipital lobes			
	R	Lingual Gyrus	18, -92, 2	185	5.14
	L	Lingual Gyrus/ Middle Occipital Gyrus	-12, 90, -1	151	5.84
RE Middle		none			
RE Late		***Frontal lobes***			
	L	Superior Frontal Gyrus	-14, 62, 28	193	4.78
	L	Middle Frontal Gyrus	-42, 20, 41	128	5.19
	L	Middle Frontal Gyrus/Middle Orbital Gyrus	-30, 62, 6	93	4.27
	L	IFG, p. Triangularis/ IFG, p. Orbitalis	-54, 28, 0	81	4.51
	L	Superior Frontal Gyrus/Middle Frontal Gyrus	-18, 24, 52	75	5.08
	R	Superior Medial Gyrus	8, 48, 33	75	4.87
	R	Superior Frontal Gyrus	22, 28, 55	57	4.35
		Parietal lobes			
	L	Inferior Parietal Cortex	-56, -54, 22	146	4.37
		Occipital lobes			
	R	Calcarine Gyrus	30, -68, 11	72	5.05
		Subcortical areas			
	Bilateral	Caudate Nucleus	-12, 18, 14	191	5.13

Table 3. Direct comparison of activations in the Early and Late components of the [Reappraisal> Watch] contrast, revealing activation unique to each time period, corrected for multiple comparisons at α<0.1 (p<0.005 & k>50). Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus

Comparison	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
RE Early>Late		***Frontal lobes***			
	Bilateral	Middle Cingulate Cortex/ pre-SMA	8, 10, 41	360	5.37
	L	Precentral Gyrus, Superior Frontal Gyrus	-22, -14, 72	272	5.28
	L	Precentral Gyrus	-40, 0, 30	202	5.93
	R	Middle Cingulate Cortex	12, 24, 44	124	4.60
	R	IFG (p. Opercularis)/Middle Frontal gyrus	40,4,25	107	4.15
		Temporal lobes			
	R	Inferior Temporal Gyrus/Fusiform Gyrus	48, -48, -11	64	3.81
	L	Middle Temporal Gyrus/Supramarginal Gyrus	-50, -46, 11	75	3.87
		Occipital lobes			
	Bilateral	Lingual Gyrus/ Calcarine Gyrus/ Fusiform Gyrus	24, -70, -8	13209	9.99
RE Late> Early		***Frontal Lobes***			
	R	Superior Frontal Gyrus	20, 28, 55	102	4.53
	R	Superior Medial Gyrus	8, 48, 30	63	4.36
		Subcortical areas			
	R	Putamen	28, -2, 11	54	4.14

Table 4. Connectivity increases for the [Reappraisal>Watch] contrast corrected for multiple comparisons at alpha<0.1 (p<0.005 & k>50). Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus

Seed	Component	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
L	RE Early	R	IFG, p. Orbitalis	34, 36, -16	56	3.99
L	RE Middle	L	IFG, p. Orbitalis	-30, 26, -6	72	5.00
L	RE Late		***Frontal lobes***			
		L	IFG, p Triangularis	-36, 18, 28	136	4.80
		R	Superior Medial Gyrus	4, 42, 38	52	5.02
R	RE Early		***Parietal lobes***			
		R	Precuneus	2, -56, 26	96	5.24
		R	Angular Gyrus	48, -56, 32	55	3.94
R	RE Middle		***Frontal lobes***			
		R	Presupplementary Motor Area	12, -12, 68	72	5.64
			Temporal lobes			
		L	Superior Temporal Gyrus	-58, -24, 2	95	3.91
R	RE Late		None			

Table 5. Direct comparison of connectivity changes in the Early, Middle and Late components of the [Reappraisal> Watch], revealing unique components of each time period. Corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$). Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus

Seed	Component	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
L	RE Early		none			
	RE Middle		***Frontal lobes***			
		L	IFG, p. Orbitalis	-24, 21, -6	116	5.01
		R	Superior Frontal Gyrus	14, -12, 72	61	4.93
		R	Anterior Insula	46, 10, -12	60	3.54
			Temporal lobes			
		R	Hippocampus/Parahippocampal Gyrus	18, -36, -4	188	4.27
	RE Late		***Frontal lobes***			
		L	Middle Frontal/ Superior Orbital Gyrus	-34, 46, 2	149	4.01
		L	IFG, p. Triangularis	-34, 18, 16	125	3.75
			Subcortical areas			
		L	Putamen	-27, 5, 3	202	5.04
		L	Caudate Nucleus/ Thalamus	-16, -8, 20	67	3.82
R	RE Early		***Frontal lobes***			
		R	IFG, p. Triangularis	42, 26, 6	82	4.71
			Temporal lobes			
		L	Middle Temporal Gyrus/ Angular Gyrus	-54, -52, 14	112	3.36
			Parietal lobes			
		L	Paracentral Lobule	-21, -29, 67	364	4.17
		R	Supramarginal Gyrus	56, -22, 24	195	4.22
		R	Postcentral Gyrus	44, -30, 52	72	3.28
		Bilateral	Precuneus	-10, -56, 68	182	4.21
			Subcortical areas			
		L	Putamen	-24, -10, 14	113	4.69
	RE Middle		***Temporal lobes***			
		L	Superior Temporal Gyrus	-48, 2, -4	82	3.51
			Subcortical areas			
		R	Caudate Nucleus	12, 4, 4	62	3.89
	RE Late		***Frontal lobes***			
		R	Superior Frontal Gyrus	28, 48, 10	107	4.11
		L	Middle Cingulate Cortex	-10, -8, 34	74	3.53
			Subcortical areas			
		R	Caudate Nucleus	20, 10, 22	59	3.81

Table 6. Whole brain results for the [Suppress> Watch] component contrasts corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$). Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus

Component	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
SE Early		***Frontal lobes***			
	R	Presupplementary Motor Area	6, -2, 61	67	4.26
	R	Anterior Insula	42, 4, 5	59	4.06
SE Middle		none			
SE Late		***Frontal lobes***			
	Bilateral	Superior Medial Gyrus/Superior Frontal Gyrus	2, 54, 22	234	4.55
	L	Middle Orbital Gyrus/ Middle Frontal Gyrus	-38, 56, -6	184	5.09
	L	Superior Medial Gyrus	-2, 34, 50	157	3.79
	Bilateral	Superior Medial Gyrus/ Anterior Cingulate Cortex	-2, 38, 8	118	4.05
	L	Middle Frontal Gyrus	-36, 14, 44	114	5.16
	L	IFG, p. Orbitalis/ IFG, p. Triangularis	-34, 20, -19	102	4.84
		Temporal lobes			
	R	Postcentral Gyrus/Rolandic Operculum	60, -4, 28	259	4.81
	L	Middle Temporal Gyrus	-59, -31, -8	59	3.70

Table 7. Direct comparison of activation in the Early and Late components of the [Suppression>Watch] contrast, corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$), revealing unique components of each time period . Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus

Comparison	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
SE Early>Late		***Frontal lobes***			
	L	Precentral Gyrus	-42, 0, 33	122	3.81
	R	Superior Frontal Gyrus	28, -8, 61	69	4.36
		Parietal lobes			
	R	Superior Parietal Lobule	22, -58, 50	133	4.61
	L	Superior/Inferior Parietal Lobule	-26, -52, 50	74	3.88
		Temporal lobes			
	Bilateral	Lingual Gyrus/ Fusiform Gyrus	22, -70, -8	7226	8.73
SE Late>Early		***Frontal lobes***			
	Bilateral	Rectal Gyrus/ ACC/ Superior Medial Gyrus	2, 48, -19	3895	5.84
	R	Middle Frontal Gyrus	32, 14, 50	238	4.45
	L	IFG, p. Orbitalis	-36, 20, -17	193	4.98
	L	Superior/Middle Frontal Gyrus	-26, 60, 8	90	4.26
	L	IFG, p. Orbitalis/Middle Orbital Gyrus	-38, 58, -8	71	3.38
	R	IFG, p. Orbitalis/ Middle Orbital Gyrus	46, 42, -6	133	4.06
		Temporal lobes			
	R	Middle/Superior Temporal Gyrus	68, -20, -17	266	4.76
	L	Superior Temporal Gyrus	-44, -26, 3	103	3.81
		Parietal lobes			
	Bilateral	Precuneus	8, -52, 22	338	4.30
	L	Angular Gyrus	-44, -60, 25	208	3.91
	R	Angular Gyrus	32, -58, 28	151	4.14
	L	Paracentral Lobule	-4, -34, 58	80	4.39

Table 8. Connectivity changes for the left insula seed [Suppression>Watch] component contrasts in the Early (0-5 sec), Middle (5-10), and Late (10-15) periods, corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$). Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus. MOG = Middle Orbital Gyrus

Seed	Component	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T- value (peak)
L	SE Early		***Frontal lobes***			
		R	Superior Medial Gyrus/ Superior Frontal Gyrus	10, 28, 52	82	5.22
		R	Middle Cingulate Cortex	10, 12, 36	52	5.23
		L	Presupplementary Motor Area	-14, -2, 66	50	3.95
L	SE Middle		***Frontal lobes***			
		Bilat.	Middle/Anterior Cingulate Cortex	10, 32, 28	883	5.85
		L	MOG/IFG, p.Triangularis/ p. Orbitalis	-34, 44, -10	245	5.35
		R	Superior Frontal Gyrus	26, 22, 44	233	5.20
		L	Middle Frontal Gyrus	-30, 54, 16	208	5.30
		R	Rolandic Operculum	64, -20, 16	95	5.34
		L	Middle Frontal Gyrus	-40, 32, 36	91	4.10
		L	Precentral Gyrus	-32, 0, 60	83	4.95
		R	IFG, p. Triangularis/ p. Opercularis	46, 24, 20	83	5.30
			Temporal lobes			
		R	Temporal Pole/ IFG, p. Triangularis/p. Orbitalis	48, 22, -16	179	5.18
		L	Superior Temporal Gyrus	-56, -44, 22	176	4.72
			Subcortical areas			
		R	Putamen	30, 6, 4	146	5.42
L	SE Late		***Frontal lobes***			
		R	Rolandic Operculum	62, -4, 16	391	4.92
		R	Presupplementary Motor Area	8, -8, 56	171	3.99
		L	Middle/ Superior Frontal Gyrus	-24, 50, 32	152	4.33
		Bilat.	Superior Frontal Gyr./Pre- SMA	2, 26, 54	138	4.46
		R	Superior Medial Gyrus	12, 52, 28	90	3.74
		L	IFG, p. Orbitalis	-40, 40, -8	88	4.88
		L	Middle Frontal Gyrus	-30, 34, 42	73	4.43
		R	Middle Frontal Gyrus	44, 20, 38	57	4.52
		R	Precentral Gyrus	38, 20, 40	108	4.57
			Temporal lobes			
		L	Superior Temporal Gyrus	-52, -42, 22	129	4.51
			Parietal lobes			
		L	Postcentral Gyrus	-52, -18, 49	80	5.05
			Subcortical areas			
		R	Putamen	30, 2, 10	65	4.76

Table 9. Connectivity changes for the right insula seed [Suppression>Watch] component contrasts in the Early (0-5 sec), Middle (5-10 sec) and Late (10-15) periods, corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$). Multiple brain regions indicate sub-maxima of clusters.

Seed	Component	Laterality	Brain Region	MNI	Extent	T- value
R	SE Early		***Frontal lobes***			
		R	Presupplementary Motor Area	6, 22, 48	153	4.40
		L	Middle Frontal/Orbital Gyrus	-36, 44, 6	114	5.46
		R	Middle Frontal Gyrus	44. 14. 50	52	5.69
		R	Middle Orbital Gyrus	32, 52, -2	51	5.09
			Temporal lobes			
		L	Middle Temporal Gyrus	-48, -52, 25	84	5.40
			Parietal lobes			
		L	Inferior Parietal Lobule	-40, -60, 52	483	6.13
		R	Angular Gyrus	46, -56, 38	84	4.05
			Occipital lobes			
		L	Posterior Cingulate Cortex	-10, -46, 22	469	4.90
			Subcortical areas			
		R	Thalamus	12, -10, 4	58	4.62
R	SE Middle & Late		None			

Table 10. Direct comparison of connectivity changes in the Early, Middle and Late components of the [Suppress> Watch] contrast, revealing unique components of each time period. Corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$). Multiple brain regions indicate sub-maxima of clusters.

Seed	Component	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
L	SE Early	R	Calcarine Gyrus/ Superior Occipital Gyrus	14, -92, 4	59	3.42
	SE Middle		***Frontal lobes***			
		R	Superior Frontal Gyrus	22, 20, 36	73	3.85
		R	Rolandic Operculum	62, -22, 14	212	4.71
			Parietal lobes			
		R	Inferior Parietal Lobule	46, -54, 52	4.10	4.10
			Occipital lobes			
		L	Calcarine Gyrus	-4, -68, 18	63	3.73
	SE Late	L	Rolandic Operculum	-44, -16, 22	67	3.83
		R	Rolandic Operculum	58, 0, 8	59	3.25
R	SE Early		***Frontal lobes***			
		L	Middle Frontal Gyrus	-36, 46, 6	132	4.00
		R	Middle Cingulate Cortex	2, 0, 32	102	3.38
		R	Middle Orbital Gyrus	30, 52, -4	97	4.44
			Temporal lobes			
		L	Superior Temporal Gyrus/ Temporal Pole	-56, 2, -6	89	3.89
			Parietal lobes			
		Bilateral	Precuneus	6, -70, 42	726	4.11
		L	Inferior Parietal Lobule/ Angular Gyrus	-46, -56, 50	525	4.43
		R	Angular Gyrus/ Supramarginal Gyrus	42, -66, 44	353	4.00
		R	Angular Gyrus	40, -50, 34	138	3.77
	SE Middle		***Frontal lobes***			
		Bilateral	Rostral Anterior Cingulate Cortex	-2, 30, 6	57	3.58
			Parietal lobes			
		L	Precuneus/ Calcarine Gyrus	-8, 48, 8	80	3.67
	SE Late		none			

Table 11. Direct comparison of RE and SE activation in the Early (0-5 sec) time period, corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$) revealing unique components of each strategy. Multiple brain regions indicate sub-maxima of clusters.

Comparison	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
RE>SE		***Frontal lobes***			
	L	pre-SMA/ Superior Frontal Gyrus	-4, 4, 61	230	3.79
	L	Mid Orbital Gyrus	-2,58,8	193	3.65
	L	Superior Frontal Gyrus	-16, 52, 36	121	3.73
	L	Superior Medial Gyrus	-2, 50, 44	94	3.74
	L	Middle Frontal Gyrus	-32, 50, 6	88	3.61
	L	Superior Medial Gyrus	-4, 68, 14	72	3.56
	L	IFG (p. Triangularis)	-52, 28, 0	58	4.51
		Occipital lobes			
	L	Precuneus	-2, 54, 17	92	3.62
	R	Middle Occipital Gyrus/Angular Gyrus	34, -70, 36	62	3.58
	L	Middle/Superior Occipital Gyrus	-30, 72, 36	75	3.25
SE>RE	R	Rolandic Operculum	64, 8, 14	143	3.99

Table 12. Direct comparison of RE and SE activity in the Late (10-15 sec) time period, corrected for multiple comparisons at $\alpha<0.1$ ($p<0.005$ & $k>50$) revealing unique components of each strategy. Multiple brain regions indicate sub-maxima of clusters. IFG = Inferior frontal gyrus. RO= Rolandic Operculum MCC= Middle Cingulate Cortex.

Comparison	Laterality	Brain Region	MNI (peak)	Extent (voxels)	T-value (peak)
RE>SE		***Frontal lobes***			
	L	Superior Frontal Gyrus	-14, 4, 50	60	4.31
		Temporal lobes			
	R	Hippocampus	16, -36, 8	59	5.43
	L	Hippocampus/Precuneus	-20, -46, 3	138	3.49
	L	Middle Temporal Gyrus	-34, -54, 25	171	5.04
	R	Superior Temporal Gyrus	36, -52, 14	58	4.91
SE>RE		***Frontal lobes***			
	Bilateral	Middle Cingulate Cortex	4, 8, 39	225	4.38
	Bilateral	Paracentral Lobule/Supplementary Motor Area	-8, -26, 74	107	4.26
	L	Rolandic Operculum	-44, -30, 14	93	4.70
	L	IFG (p. Triangularis)/ Middle Frontal Gyrus	-42, 34, 17	73	3.6
	L	Precentral Gyrus	-22, -16, 72	64	4.96
		Temporal lobes			
	L	Temporal Pole/Insula/RO/Putamen	-56, 10, -8	631	4.93
	L	Hippocampus/Parahippocampal Gyrus	-32, -36, -11	69	3.85
	L	Fusiform Gyrus	-22, -56, 0	61	3.65
		Parietal lobes			
	R	Supramarginal gyrus/ RO/ Superior Temporal Gyrus	58, -32, 30	1186	5.41
	R	MCC/Inferior Parietal Lobule/Postcentral Gyrus	14, -34, 47	649	6.41
	L	Supramarginal Gyrus	-62, -32, 25	163	4.40
	R	Precuneus	12, -48 , 63	86	3.96
	L	Superior/Inferior Parietal Lobule	-26, -42, 58	78	4.35
	L	Postcentral Gyrus	-60, -14, 39	76	4.13
	L	Postcentral Gyrus	-48, -18, 52	70	3.7
	L	MCC/ Precuneus/Superior Parietal Lobe	-8, -36, 52	921	5.94
		Subcortical areas			
	L	Putamen	-2, 6, 3	78	4.34
	R	Thalamus	18, -12, 00	76	4.73